



CORPORATE

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# 2024 Research & Development Day

April 25, 2024

Nasdaq: ALDX



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**Todd C. Brady, M.D., Ph.D., Chief Executive Officer, Aldeyra Therapeutics**

# Welcome and Opening Remarks

# Disclaimers and Forward-Looking Statements

This presentation and various remarks which may be made during this presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and Section 21E of the Securities Exchange Act of 1934, as amended, including statements regarding Aldeyra's future expectations, plans and prospects, including, without limitation, statements regarding: the goals, opportunity, and potential for reproxalap, ADX-2191, ADX-246, ADX-248, and ADX-629; anticipated clinical or regulatory milestones for reproxalap, ADX-2191, ADX-246, ADX-248, and ADX-629; FDA agreement with the clinical development plan for reproxalap; expectations regarding the results of scheduled FDA meetings and discussions, clinical trial initiations and completions, and the timing and nature of NDA or other submissions to the FDA; Aldeyra's business, research, development and regulatory plans or expectations; and the structure, timing and success of Aldeyra's planned or pending clinical trials. The results of earlier preclinical or clinical trials may not be predictive of future results. Forward-looking statements include all statements that are not historical facts and, in some cases, can be identified by terms such as "may," "might," "will," "objective," "intend," "should," "could," "can," "would," "expect," "believe," "anticipate," "project," "on track," "scheduled," "target," "design," "estimate," "predict," "contemplates," "likely," "potential," "continue," "ongoing," "aim," "plan," or the negative of these terms, and similar expressions intended to identify forward-looking statements.

Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause Aldeyra's actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. These statements reflect Aldeyra's current views with respect to future events and are based on assumptions and subject to risks and uncertainties, including the development of, and clinical and regulatory plans or expectations for Aldeyra's investigational new drugs (including reproxalap, ADX-2191, ADX-246, ADX-248, and ADX-629), and systems-based approaches, later developments with the FDA that may be inconsistent with Aldeyra's expectations and beliefs, including the risk that the results from earlier clinical trials, portions of clinical trials, or pooled clinical data may not accurately predict results of subsequent trials or the remainder of a clinical trial for the same or different indications, inconsistent expectations regarding FDA acceptance and review of the company's filings and submitted data sets, and Aldeyra's continuing or post-hoc review and quality control analysis of clinical data. Important factors that could cause actual results to differ materially from those reflected in Aldeyra's forward-looking statements are described in Aldeyra's most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q, as well as Aldeyra's subsequent filings with the Securities and Exchange Commission. All of Aldeyra's development plans and timelines may be subject to adjustment depending on funding, recruitment rate, regulatory review, which regulatory review timeline may be flexible and subject to change based on the regulator's workload and other potential review issues, preclinical and clinical results, regulatory developments in the United States and other countries, and other factors any of which could result in changes to Aldeyra's development plans and programs or delay the initiation, enrolment, completion, or reporting of clinical trials.

In addition to the risks described above and in Aldeyra's other filings with the SEC, other unknown or unpredictable factors also could affect Aldeyra's results. No forward-looking statements can be guaranteed, and actual results may differ materially from such statements. The information in this presentation is provided only **as of April 25, 2024**, and Aldeyra undertakes no obligation to update any forward-looking statements contained in this presentation on account of new information, future events, or otherwise, except as required by law.

# Agenda

	<b>TOPIC</b>	<b>PRESENTER</b>
9:00 – 9:45 a.m.	<b>Opening Remarks, RASP Overview, and Reproxalap Dry Eye Disease Development Plan</b>	<b>Todd C. Brady, M.D., Ph.D.</b> Chief Executive Officer, Aldeyra Therapeutics
9:45 – 10:30 a.m.	<b>Next-Generation RASP Modulators</b>	<b>Adam Brockman, Ph.D.</b> Senior Director Translational Science, Aldeyra Therapeutics
10:30 – 10:45 a.m.	<b>Break</b>	
10:45 – 11:30 a.m.	<b>Retinitis Pigmentosa Overview</b>	<b>Ramiro S. Maldonado MD</b> Ophthalmologist, Duke Center for Ophthalmic Genetics
11:30 a.m. – 12:00 p.m.	<b>ADX-2191 for the Treatment of Retinitis Pigmentosa</b>	<b>Todd C. Brady, M.D., Ph.D.</b>
12:00 – 12:30 p.m.	<b>Lunch</b>	
12:30 – 1:00 p.m.	<b>Pipeline, Milestones, and Concluding Remarks</b>	<b>Todd C. Brady, M.D., Ph.D.</b>

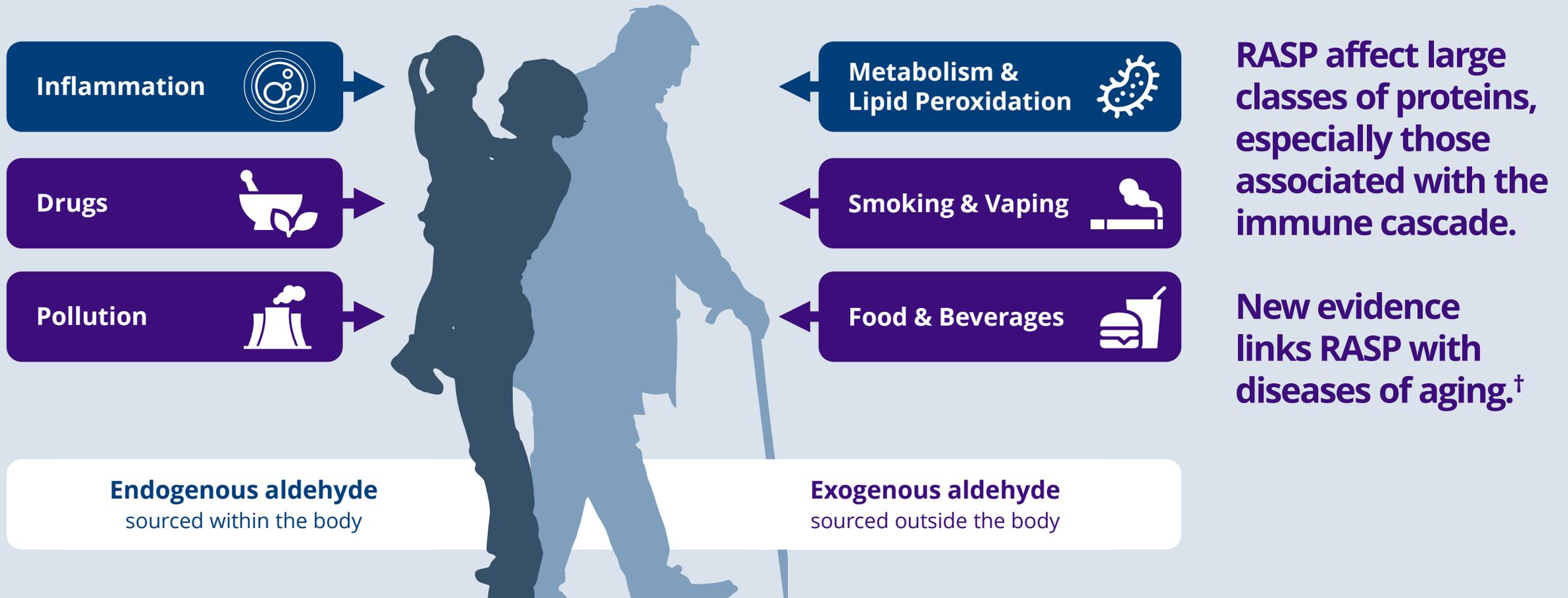


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**Todd C. Brady, M.D., Ph.D., Chief Executive Officer, Aldeyra Therapeutics**

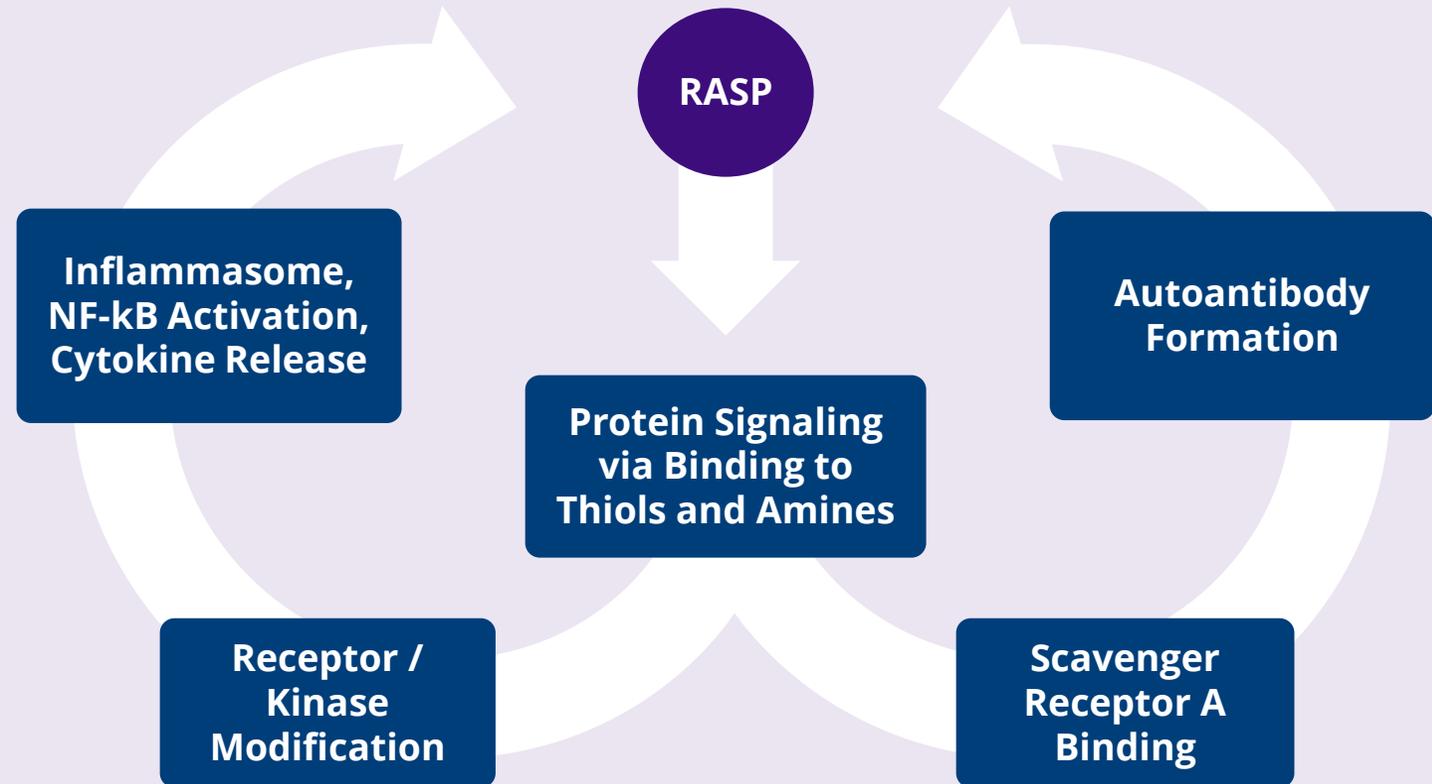
# RASP Overview

# RASP Are Toxic, and Represent a Novel, Potentially Broadly Applicable Pharmaceutical Target



# RASP Induce Inflammation via Multiple Mechanisms

- Aldehydes **covalently bind** thiol (Michael addition) and amine (Schiff base) residues on proteins.
- Direct protein binding leads to **conformational and functional** changes in proteins, which in turn initiate a pro-inflammatory signaling cascade.
- Aldehyde-protein adducts are ligands for **Scavenger Receptor A**, subsequently leading to autoantibody formation against the adducted protein.



# RASP Modulation Represents a Novel Pharmacology

**Traditional pharmacology targets specific proteins and is generally limited to two actions: on or off.**



Activating or inhibiting specific proteins on a sustained basis, which rarely occurs in nature, may lead to toxicity and could limit activity.



**RASP modulation may allow for control of protein *systems*, without turning any single protein on or off.**



Systems-based pharmacology could potentially lead to broader-based activity with less toxicity associated with activation or inhibition of specific proteins.



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**Todd C. Brady, M.D., Ph.D., Chief Executive Officer, Aldeyra Therapeutics**

# Reproxalap Dry Eye Disease Development Plan

# Phase 3 Clinical Trial of Reproxalap in a Dry Eye Chamber†

## Design

- Randomized, double-masked, vehicle-controlled dry eye chamber challenge

## Dosing

- Visit 1: Medical screening
- Visit 2: Vehicle dry eye chamber (dosing just before and 50 minutes after entry)
- Visit 3: Four doses of randomized treatment (reproxalap or vehicle)
- Visit 4: Randomized dry eye chamber (dosing just before and 50 minutes after entry)

## Size

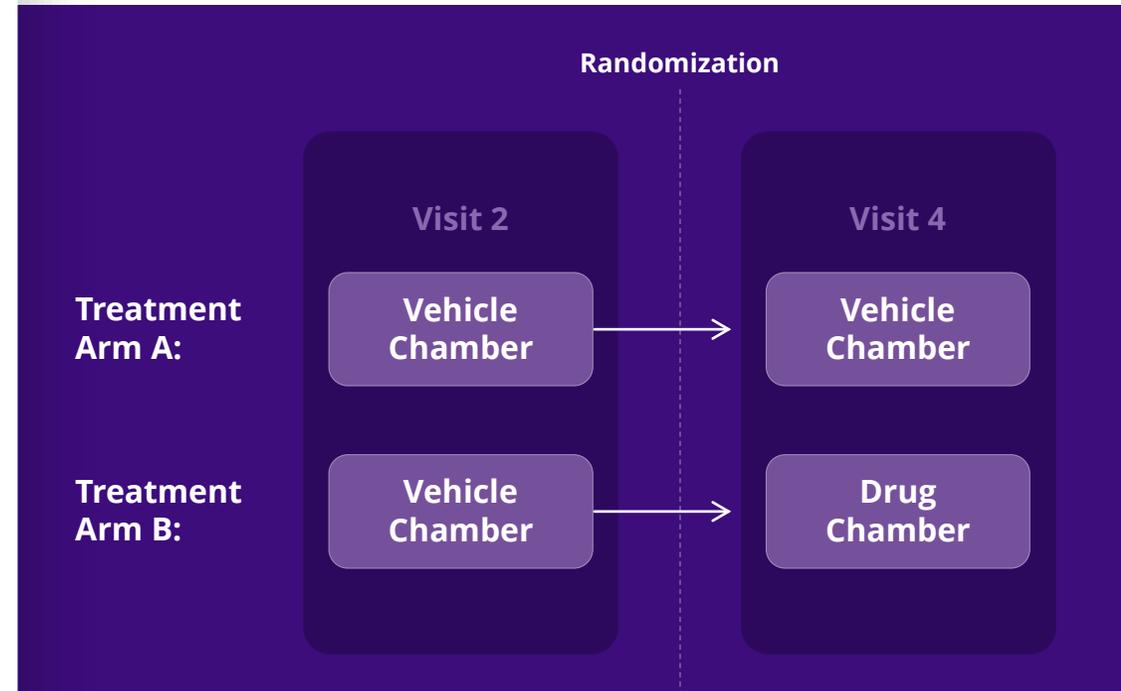
~100 dry eye disease patients

## Primary Endpoint

Ocular discomfort score

## Other Endpoints

Safety

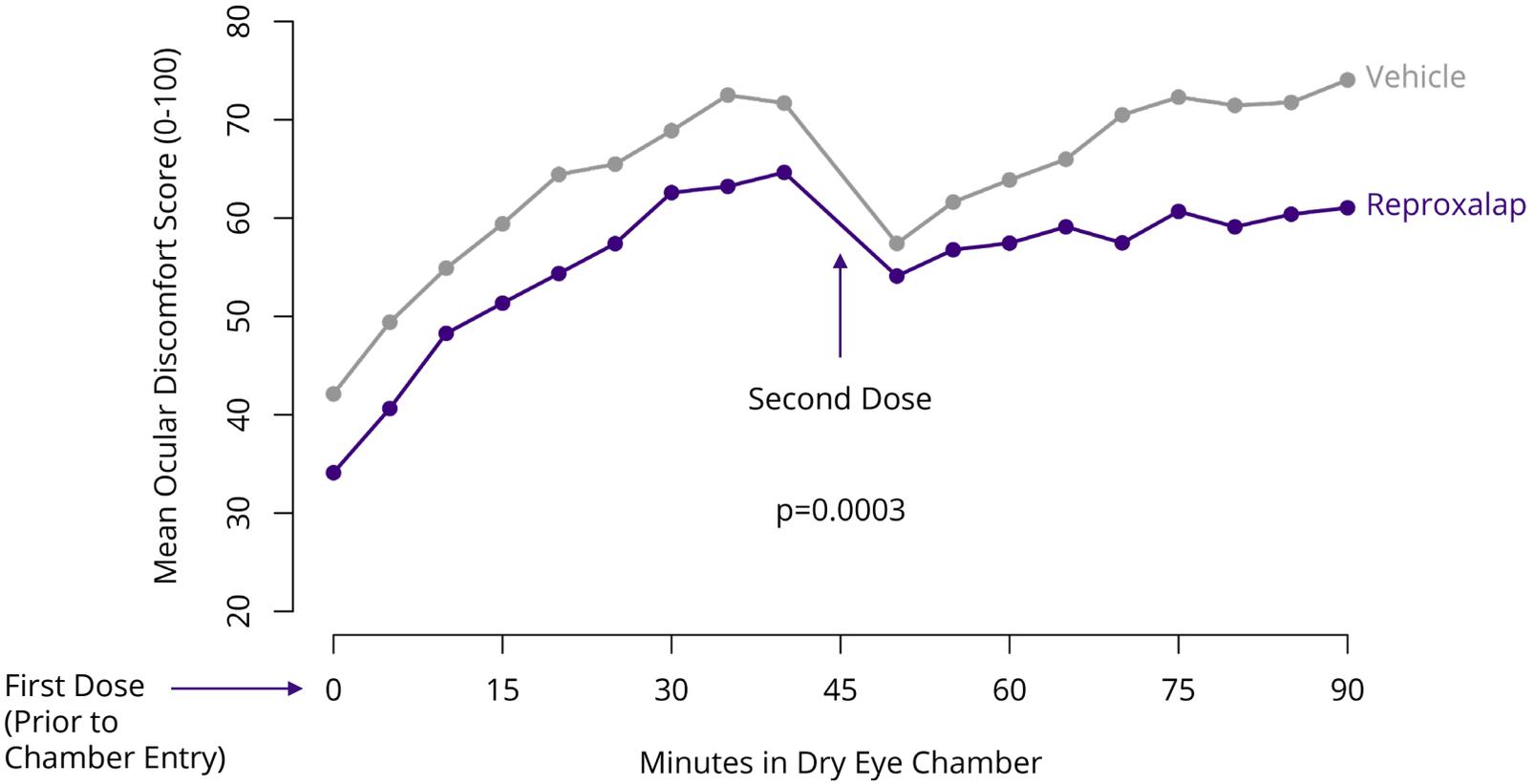


**Pending clinical trial results, feedback from ongoing FDA discussions, and other factors, NDA resubmission expected in H2 2024†‡**



†The timing of clinical trials depends, in part, on the availability of clinical research facilities and staffing, the ability to recruit patients, and the number of patients in the trial.  
‡Regulatory review and discussion timelines are flexible and subject to change based on the regulator's workload and other potential review issues.

# Based on Pooled Data from Four Dry Eye Chamber Trials, Ocular Discomfort Score was Lower with Reproxalap than with Vehicle



Ocular discomfort data are derived from four previously completed dry eye chamber clinical trials of reproxalap vs. vehicle, encompassing approximately 110 patients and incorporating trial conduct and statistical analysis amendments.

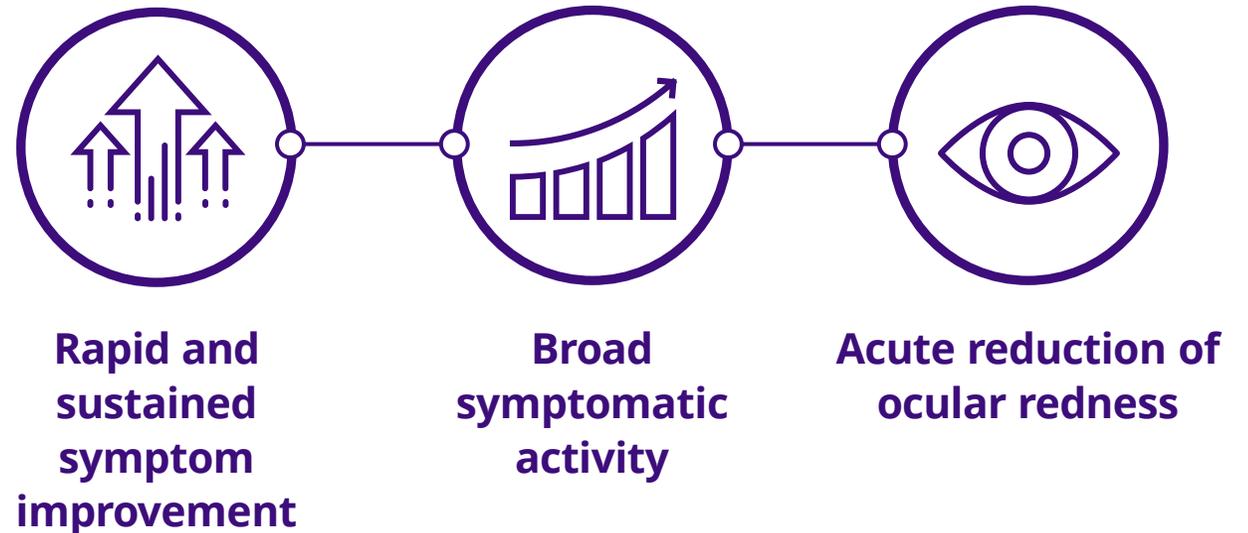


Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 2,400 patients with no observed safety concerns; mild and transient instillation site irritation is the most commonly reported adverse event in clinical trials.



# Reproxalap Represents a Novel Potential Therapeutic Approach in Dry Eye Disease with Rapid Activity in Clinical Trials

Potential advantages for patients and healthcare providers could effect a paradigm shift relative to standard of care.



**Dry eye disease afflicts 39 million or more adults in the United States.<sup>†</sup>**



<sup>†</sup>Company estimates and Am J Ophthalmol. 2014;157(4):799-806. Topical ocular reproxalap is an investigational new drug candidate that has been studied in more than 2,400 patients with no observed safety concerns; mild and transient instillation site irritation is the most commonly reported adverse event in clinical trials.

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The background features a complex network of glowing white nodes and lines, resembling a molecular structure or a data network. The nodes vary in size and brightness, with some appearing as bright white spheres and others as smaller, dimmer dots. The lines connecting them are thin and white, creating a web-like pattern that extends across the entire frame. The overall color scheme is a gradient of purple, from a darker shade on the left to a lighter, more vibrant shade on the right.

  
aldeyra

Questions

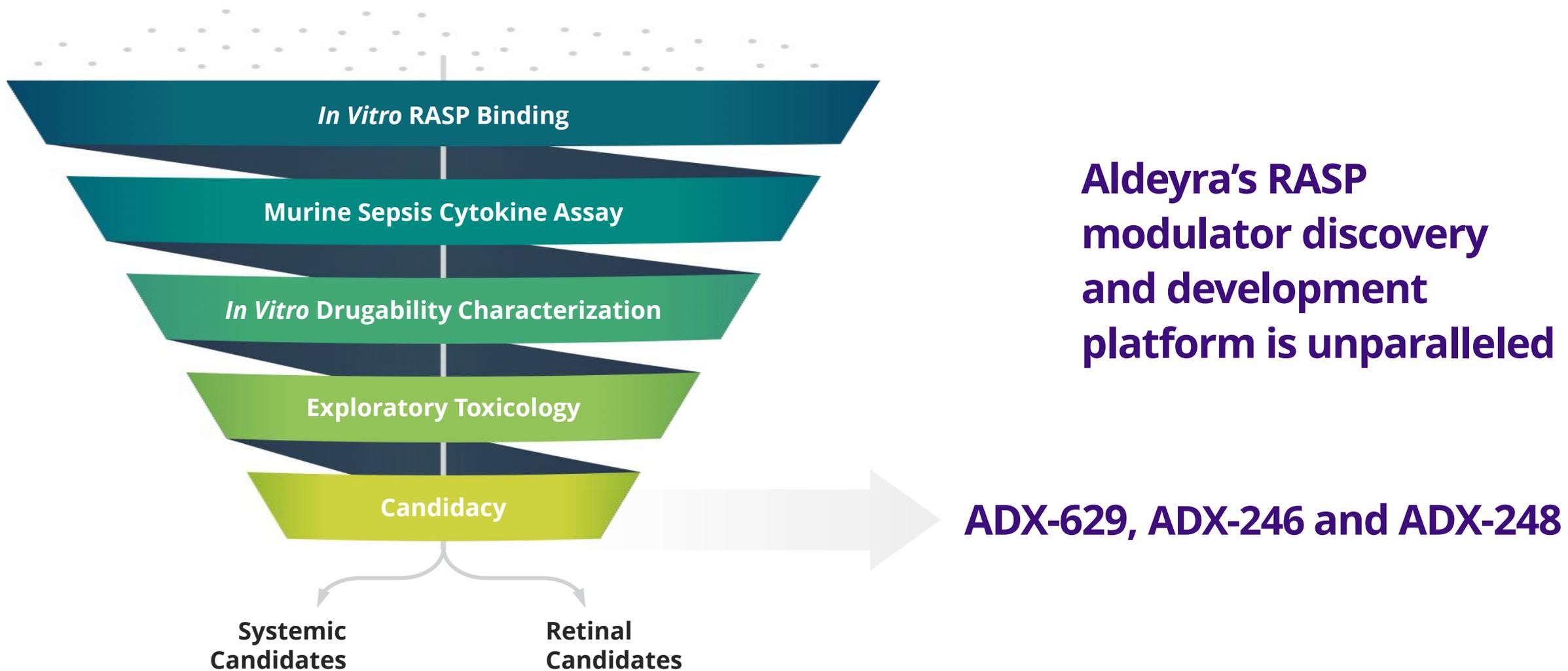


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**Adam Brockman, Ph.D., DABT, Senior Director of Translational Science, Aldeyra Therapeutics**

# Next-Generation RASP Modulators

# Aldeyra Has Developed the Leading RASP Modulator Discovery Platform



# Development Indications for New RASP Modulators Are Supported by Mechanistic Rationale

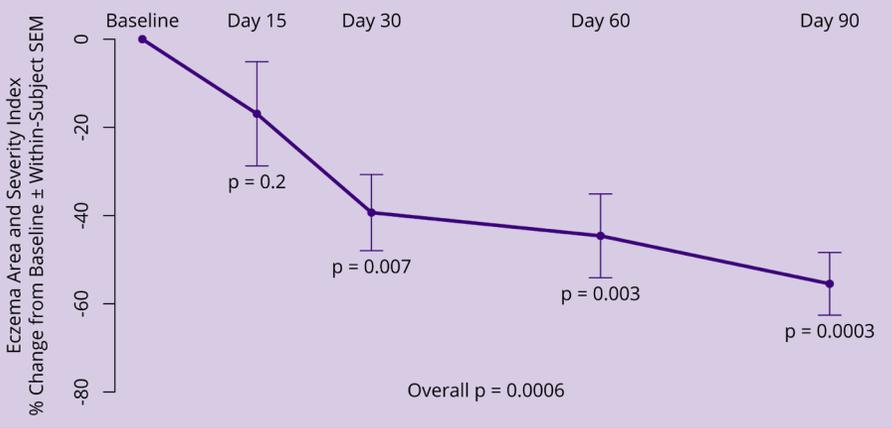
INDICATION	RASP RATIONALE	MODEL
<b>Atopic Dermatitis</b>	Upregulation of pro-inflammatory cytokines	Oxazolone atopic dermatitis
<b>Alcoholic Hepatitis</b>	Association with hepatotoxicity	Ethanol toxicity
<b>Non-Opiate Analgesia</b>	Activation of TRPV1 and TRPA1 pain receptors	Carrageenan inflammatory pain
<b>Lipogenesis Modulation</b>	Potentiation of lipid synthesis	Diet-induced obesity



Atopic Dermatitis

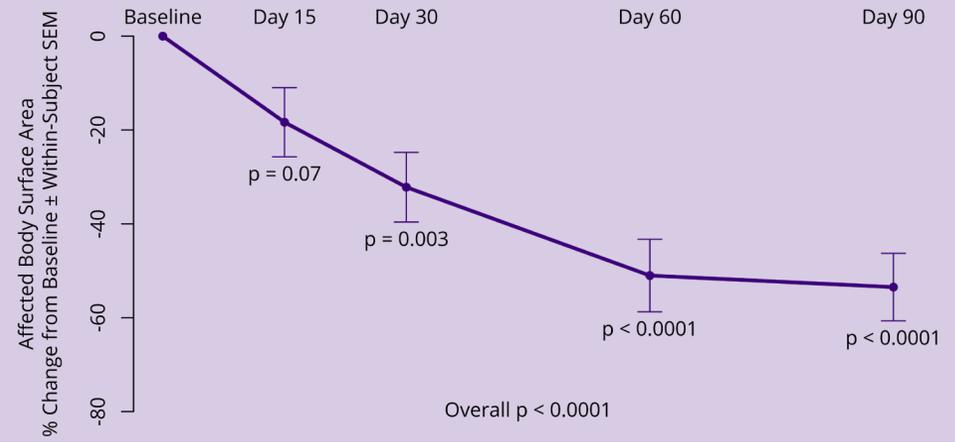
# Statistical and Clinically Significant Improvement was Observed in Phase 2 Clinical Trial of RASP Modulator ADX-629 in Atopic Dermatitis

## Eczema Area and Severity Index (EASI)

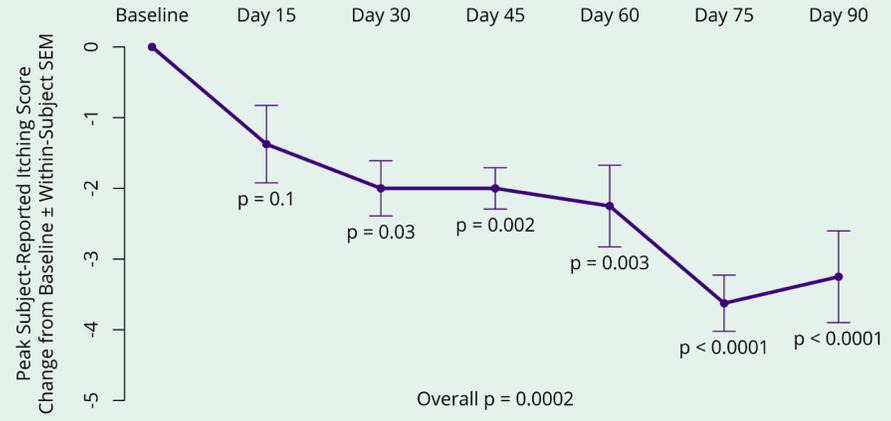


Investigator-Assessed

## Investigator Global Assessment

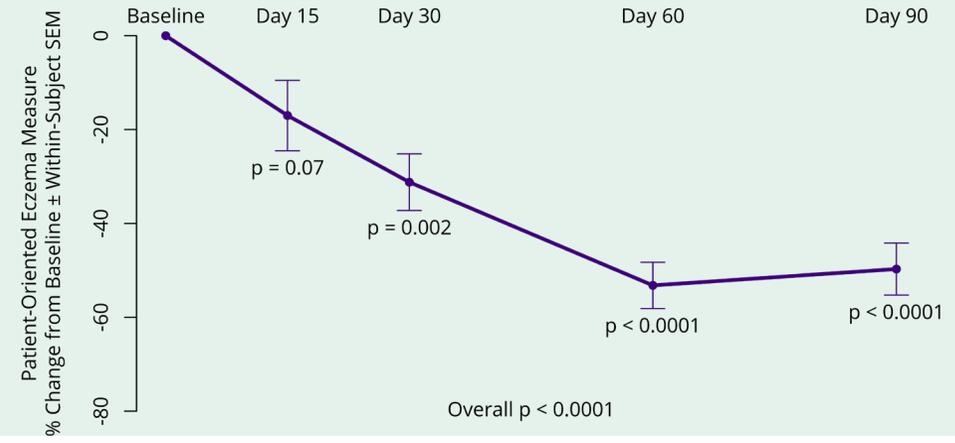


## Patient-Reported Itching Score

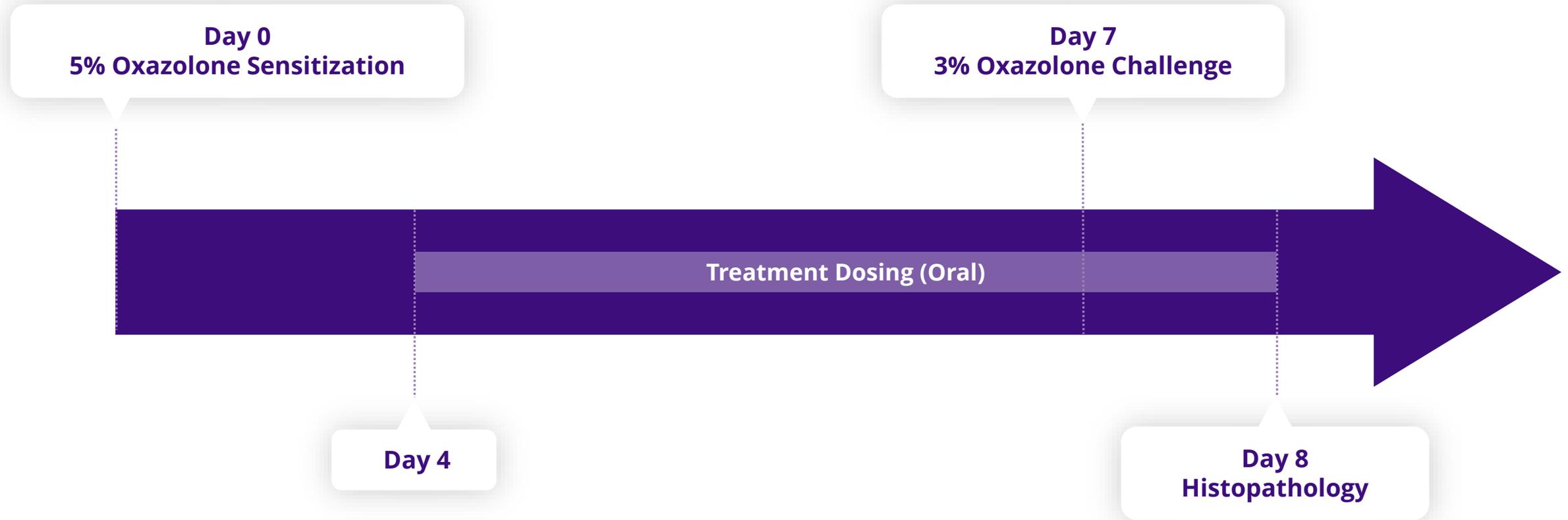


Patient-Reported

## Patient-Oriented Eczema Measure

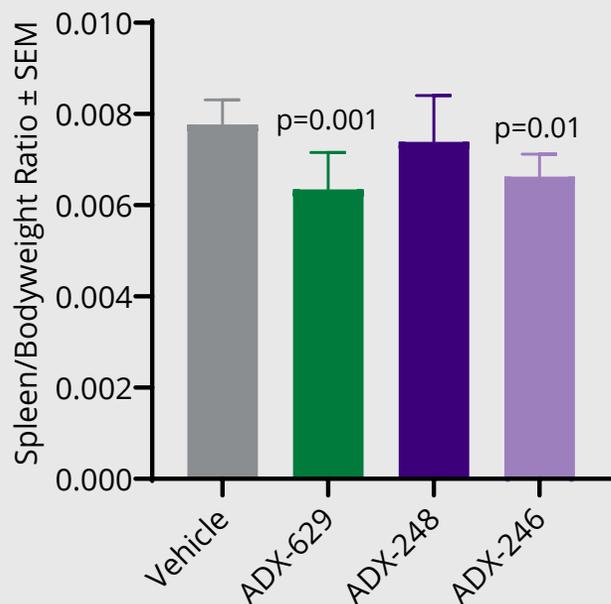


# Oxazolone Sensitization is a Well-Characterized Preclinical Model of Atopic Dermatitis

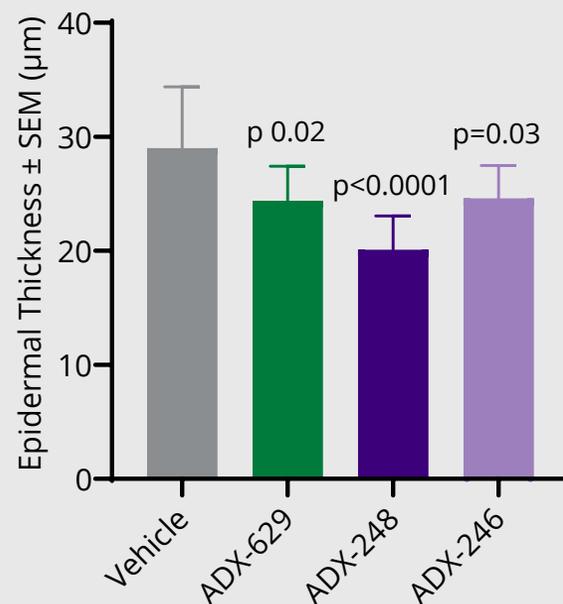


# RASP Modulators ADX-629, ADX-248, and ADX-246 Reduced Histopathology and Spleen Weight in a Preclinical Model of Atopic Dermatitis

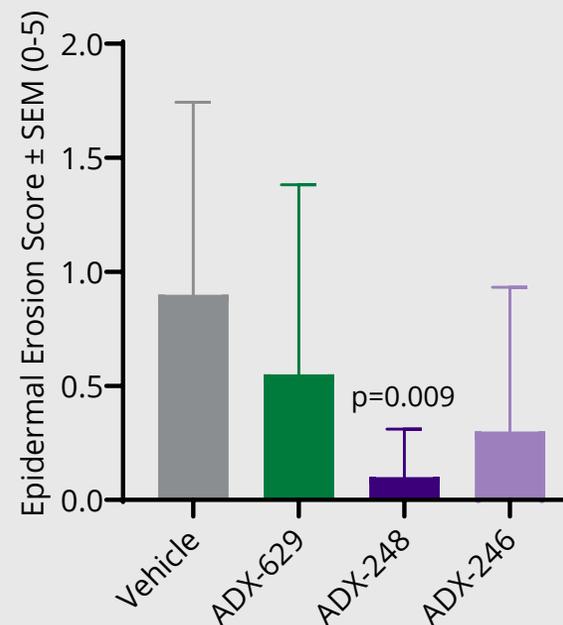
## Weight



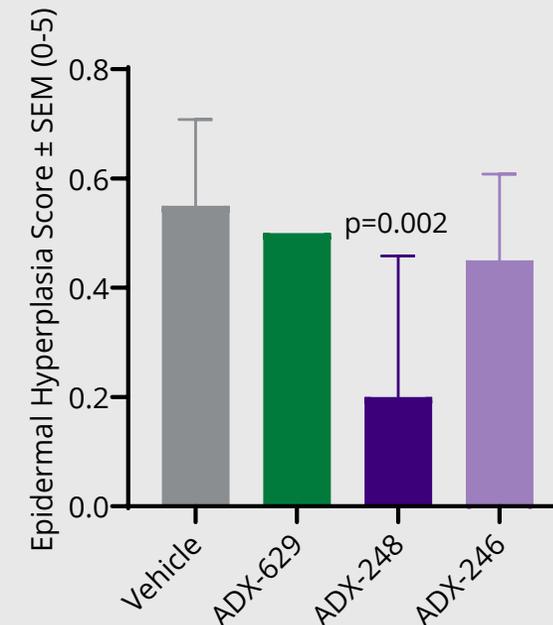
## Thickness



## Erosion



## Proliferation

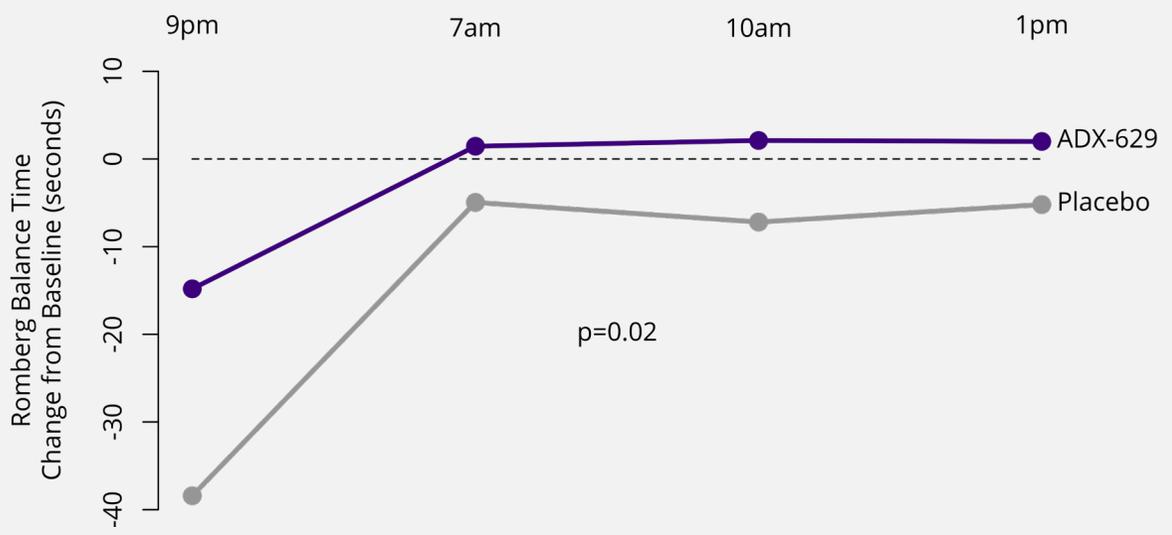




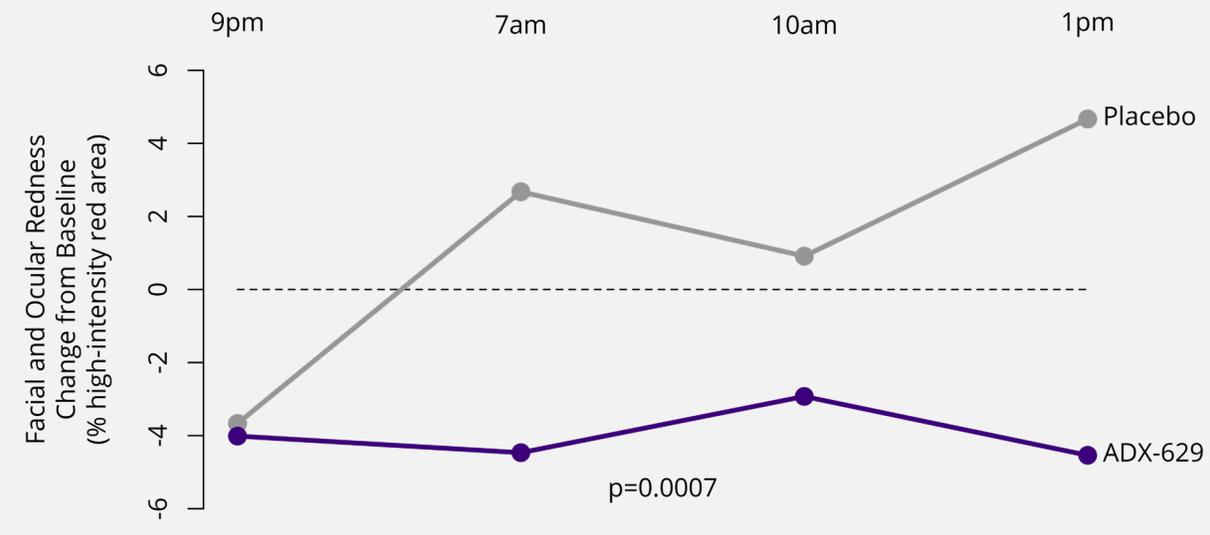
# Alcoholic Hepatitis

# ADX-629 Improved Balance and Reduced Dermal Flushing and Acetaldehyde Levels in Phase 1/2 Ethanol Toxicity Clinical Trial

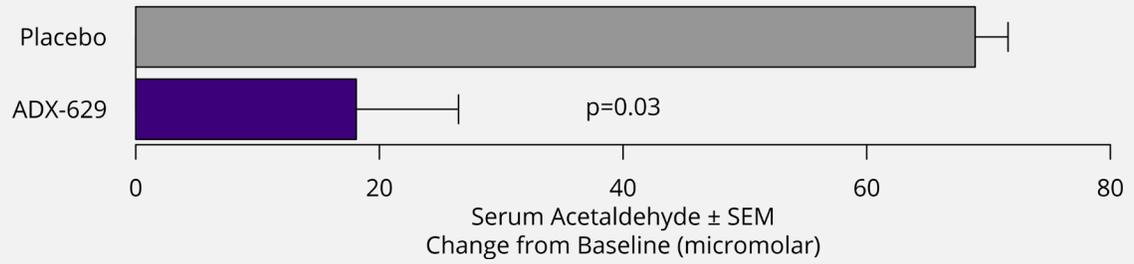
## Balance



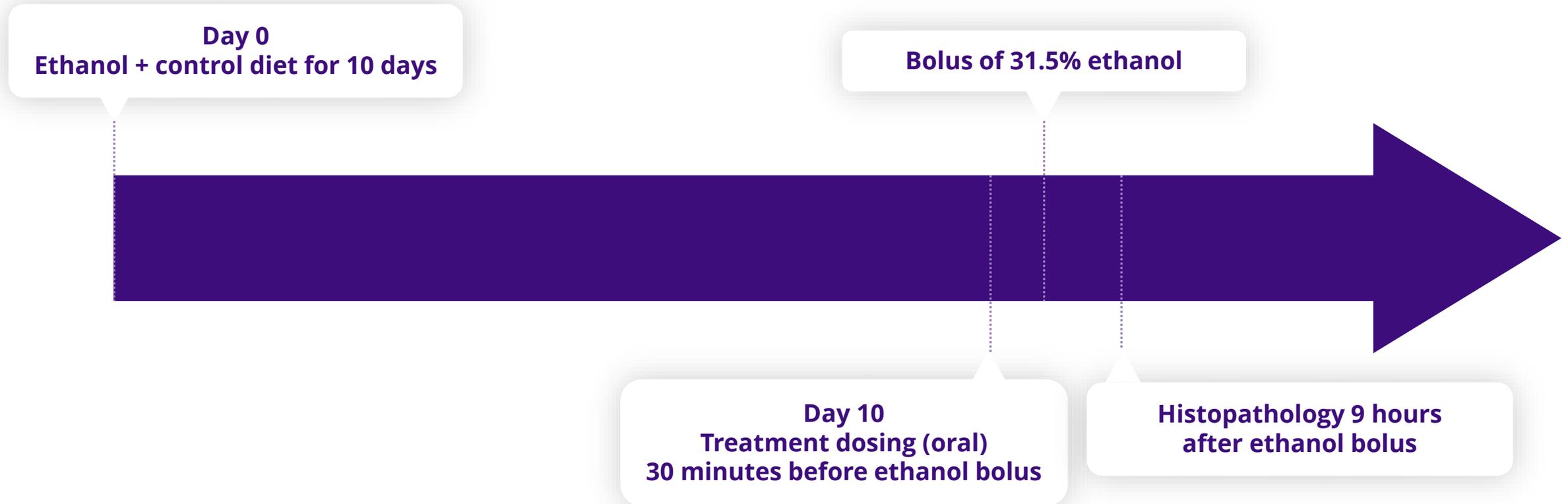
## Flushing



## Acetaldehyde

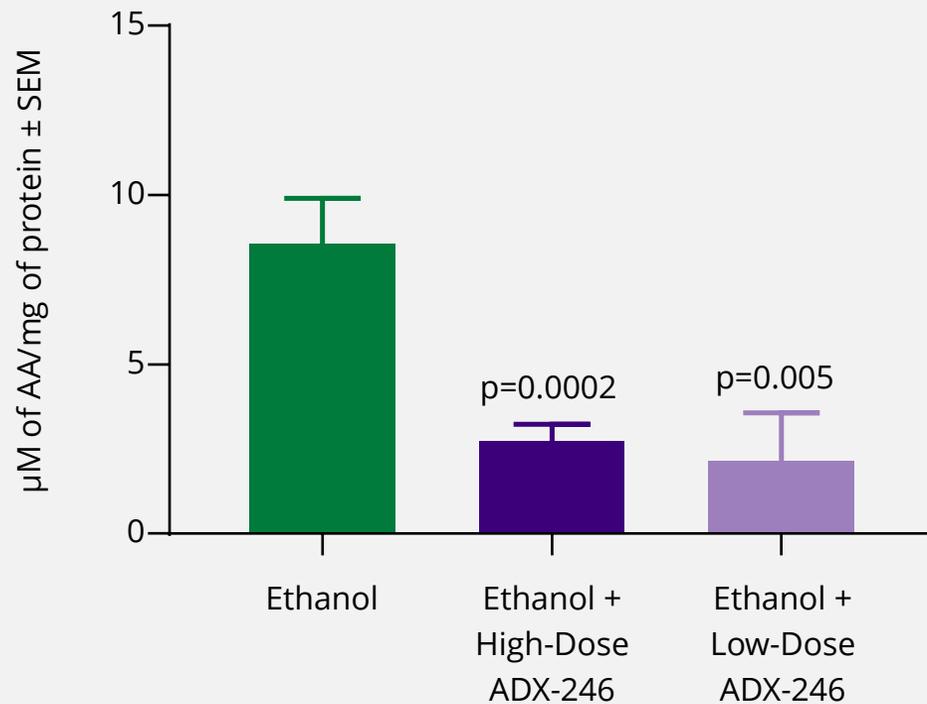


# Preclinical Model of Ethanol-Induced Hepatitis Enables Detailed Assessment of the Pharmacodynamic Activity of RASP Modulation

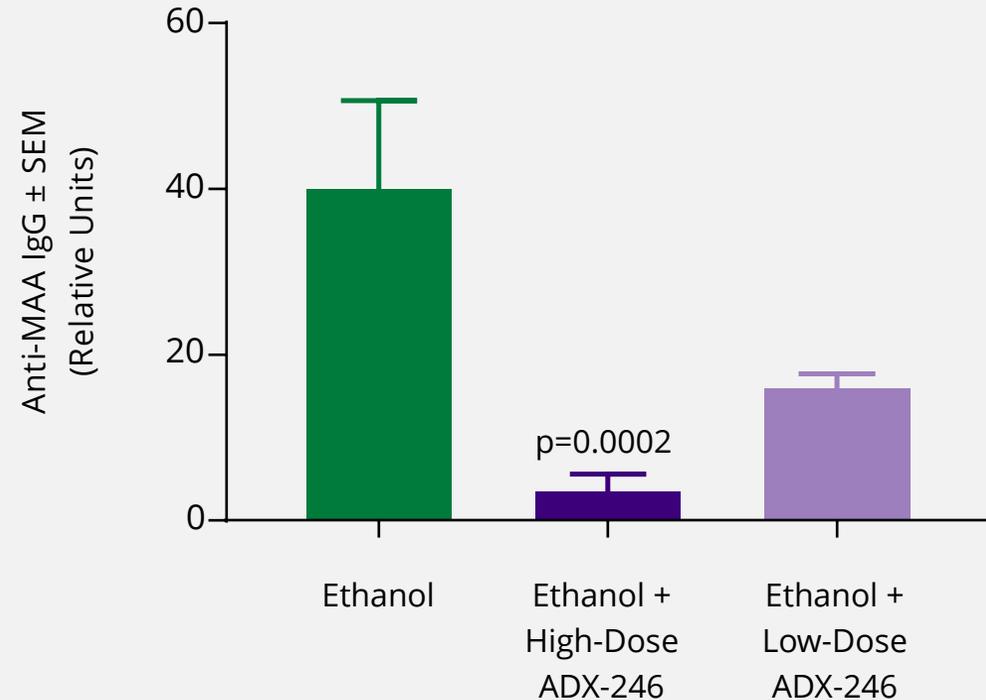


# ADX-246 Decreased RASP Levels in Preclinical Model of Ethanol-Induced Hepatitis

## Liver Acetaldehyde



## Serum Anti-Malondialdehyde Acetaldehyde Adduct



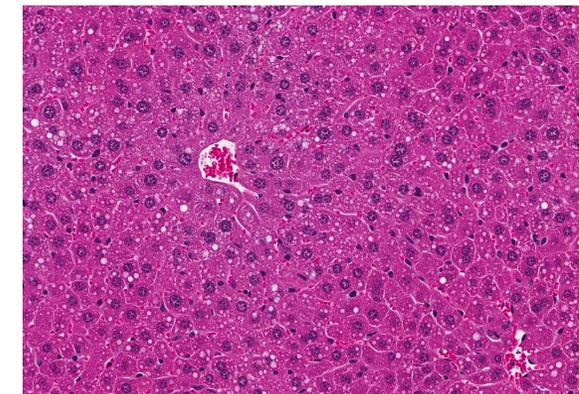
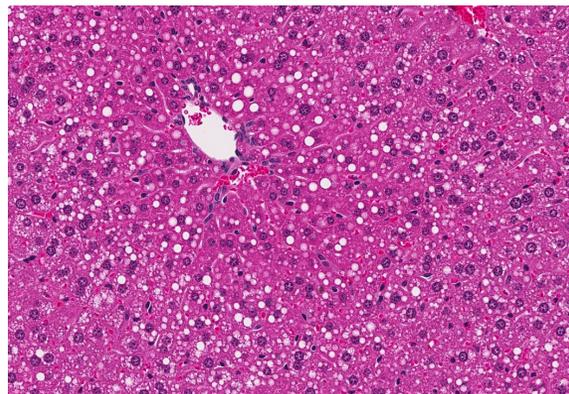
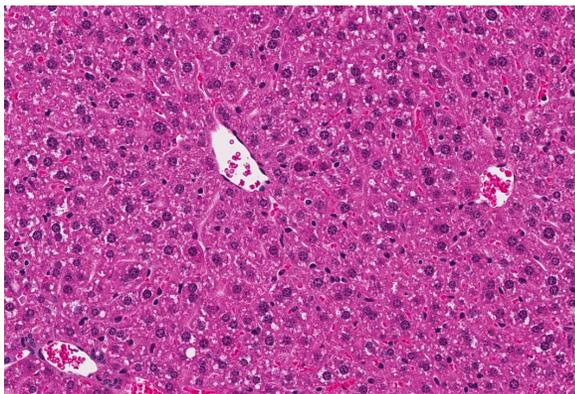
# ADX-246 Diminished Histopathological Changes in Preclinical Model of Ethanol-Induced Hepatitis

**Control**

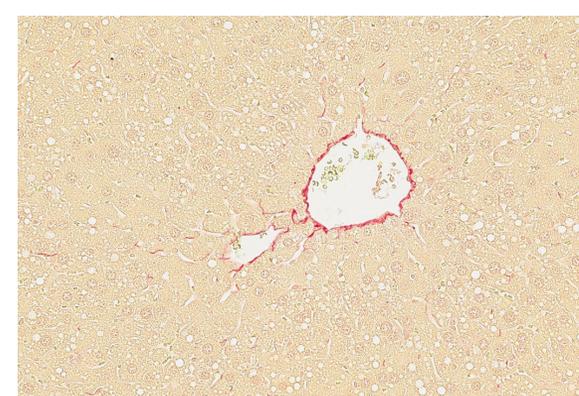
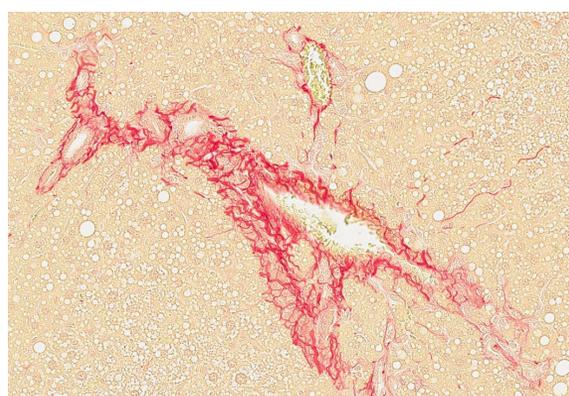
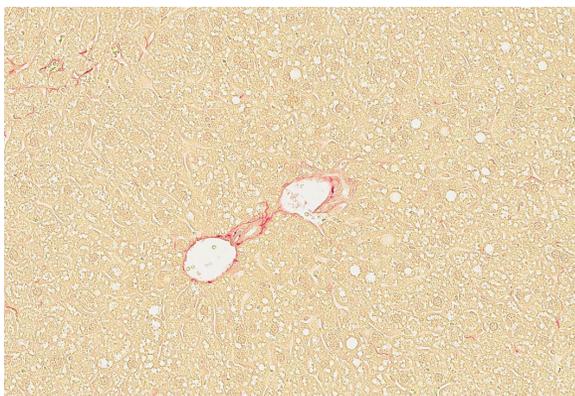
**Ethanol**

**Ethanol + ADX-246**

**Hematoxylin  
and Eosin  
Staining**



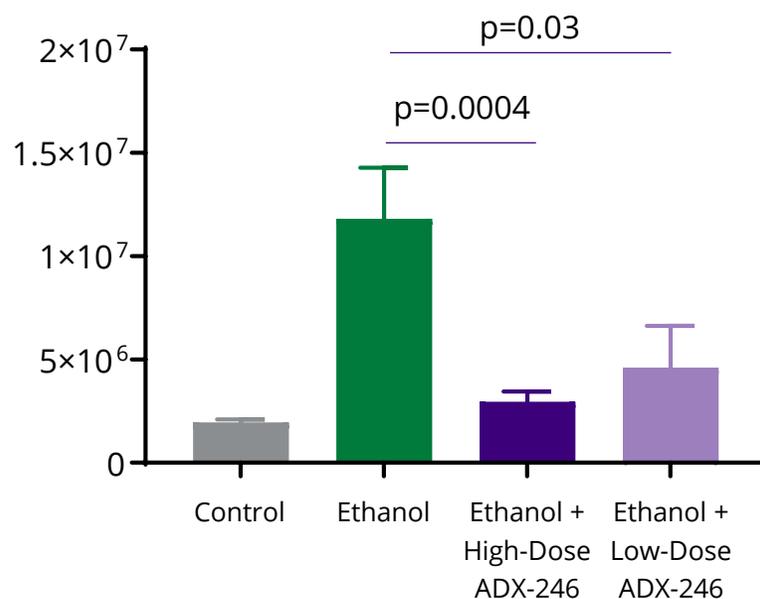
**Sirus Red  
Staining**



# ADX-246 Reduced Hepatic Levels of Lipids and Collagen in Preclinical Model of Ethanol-Induced Hepatitis

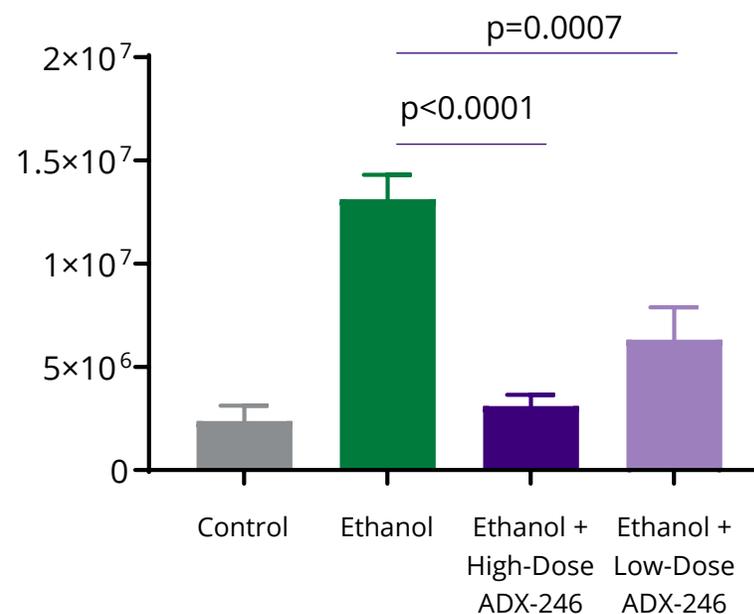
## Collagen

Integrated Density  $\pm$  SEM  
(pixels)



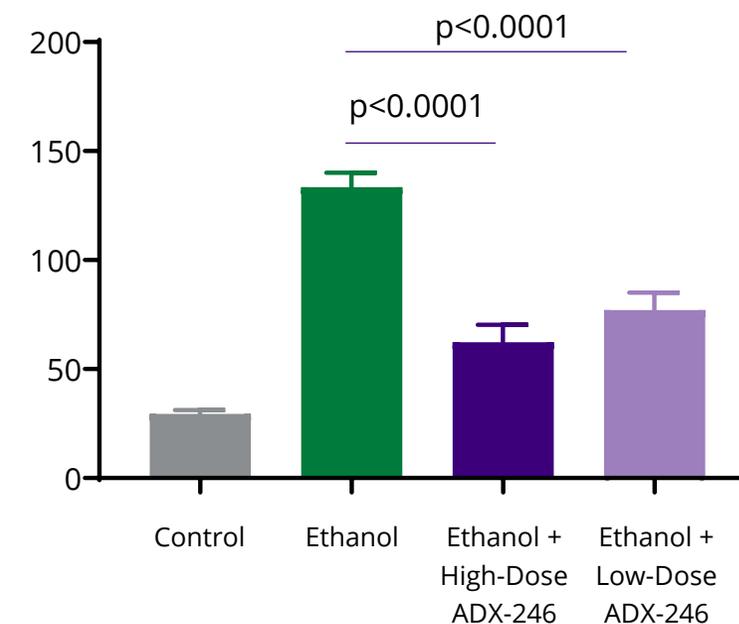
## Total Lipids

Integrated Density  $\pm$  SEM  
(pixels)



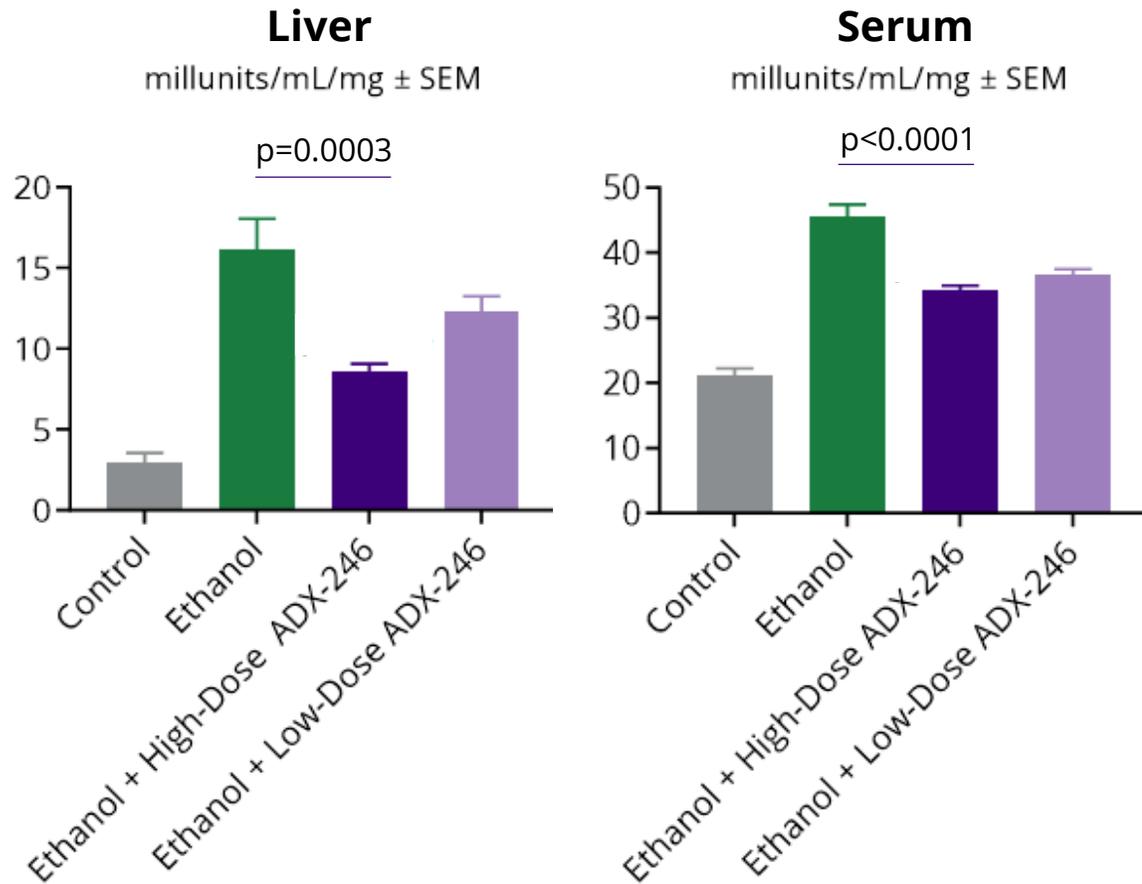
## Triglycerides

mg/dL Triglycerides per  
mg Protein  $\pm$  SEM

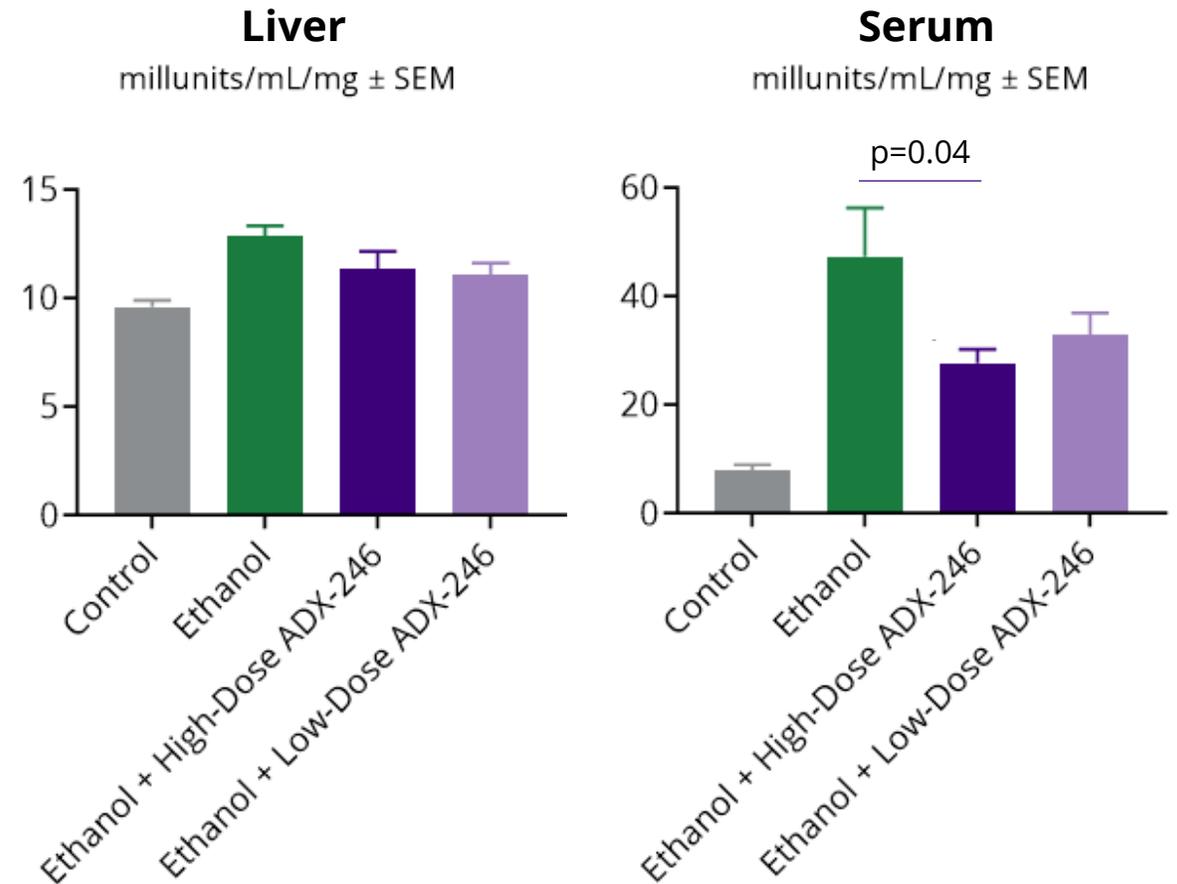


# ADX-246 Improved Liver Function Tests in Preclinical Model of Ethanol-Induced Hepatitis

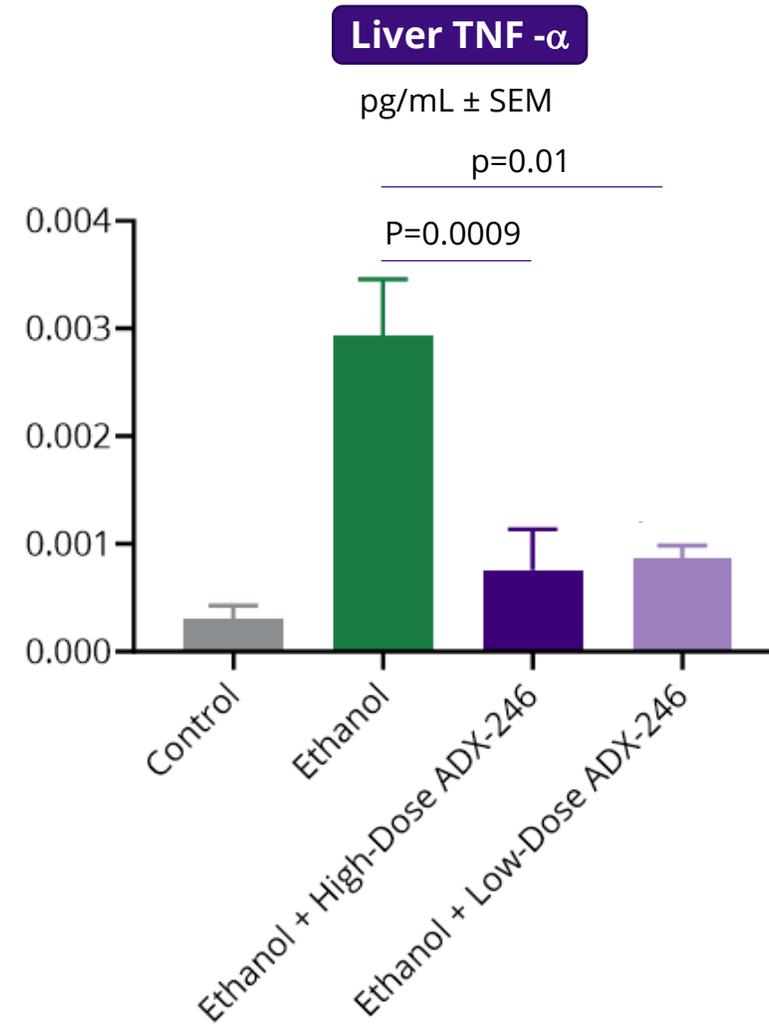
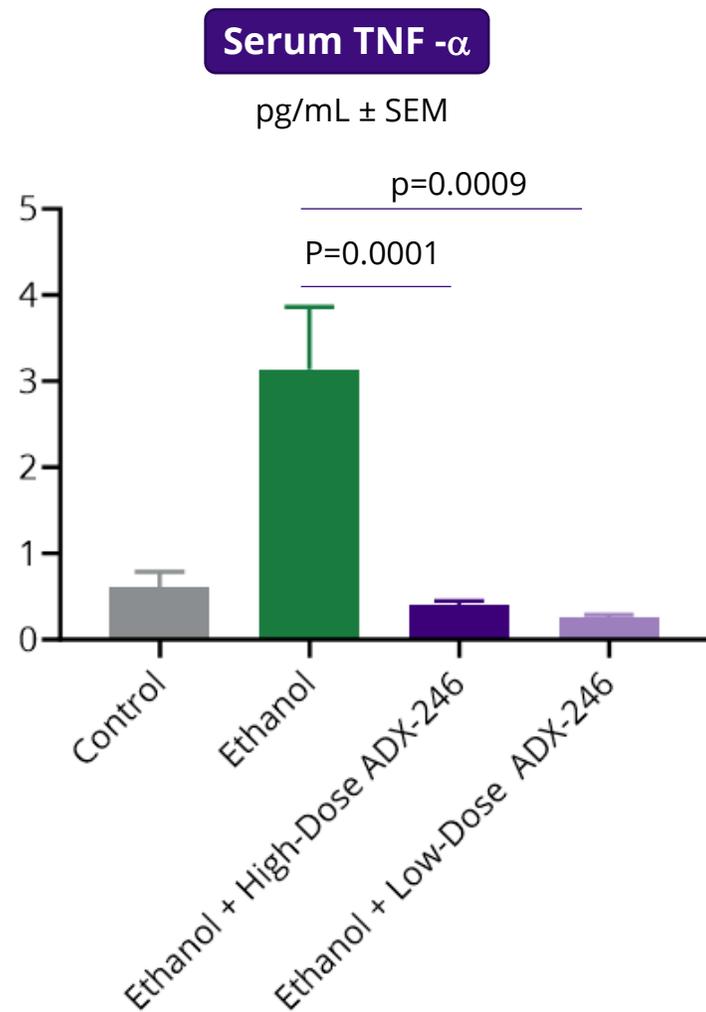
## Aspartate Aminotransferase (AST)



## Alanine Aminotransferase (ALT)



# ADX-246 Decreased Levels of the Inflammatory Cytokine TNF- $\alpha$ in Preclinical Model of Ethanol-Induced Hepatitis



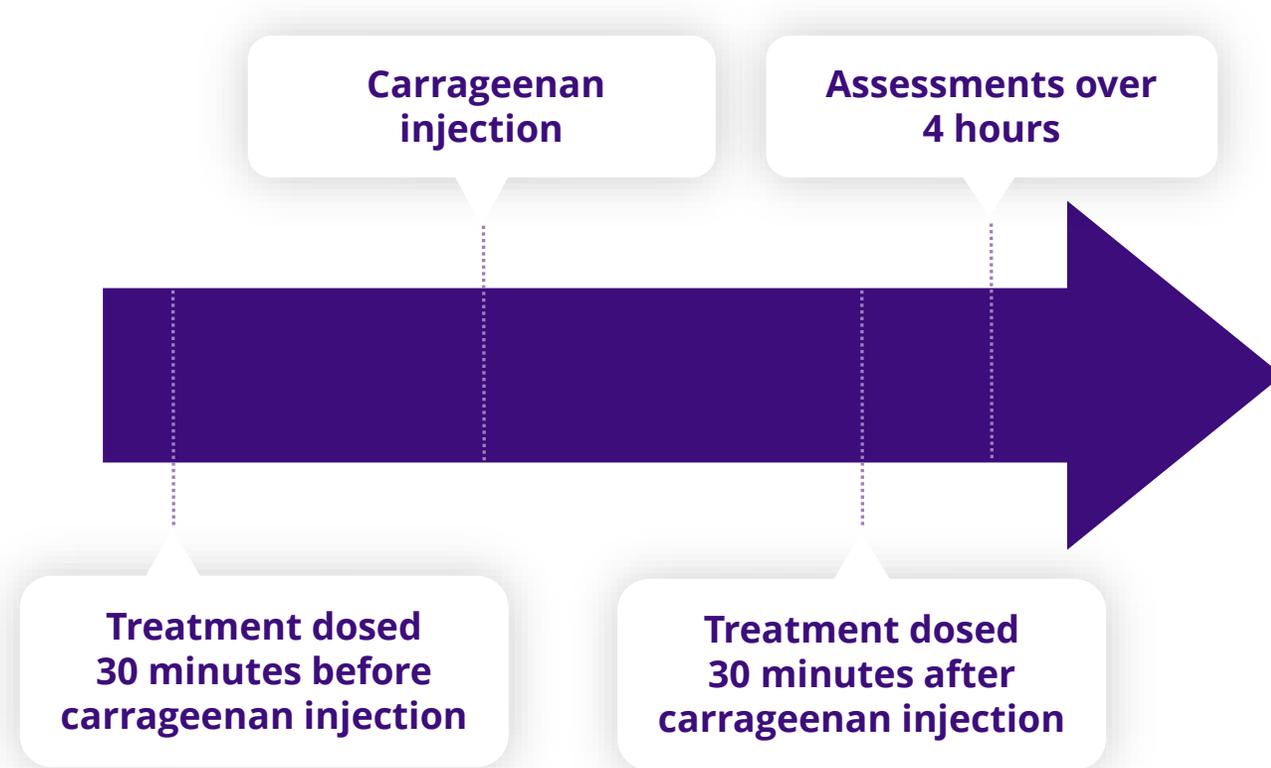


# Non-Opiate Analgesia

# The Carrageenan Inflammatory Pain Model Allows for Evaluation of Three Different Outcomes Associated with Inflammation

Test	Model	Assessment (units)
<b>Von Frey</b>	Mechanical Pain Tolerance	Force required for paw withdrawal (grams)
<b>Hargreaves</b>	Thermal Pain Tolerance	Time to withdrawal in response to heat (seconds)
<b>Ankle Caliper</b>	Swelling	Diameter of ankle (millimeters)

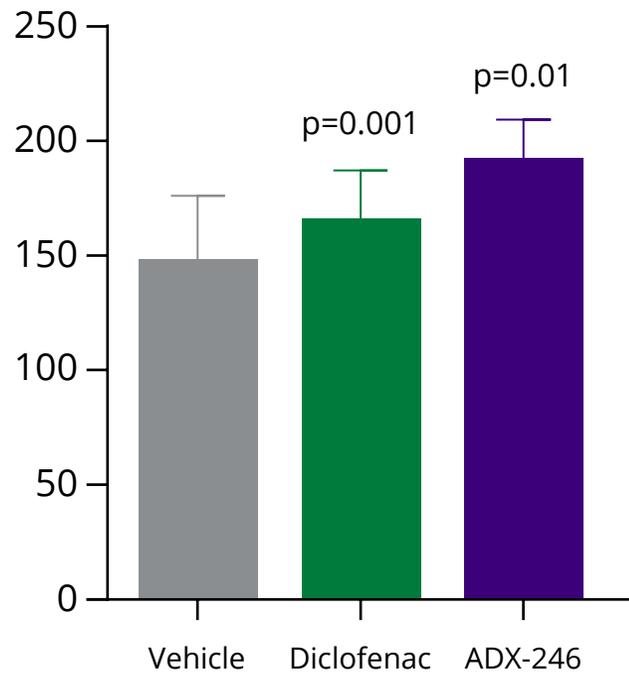
## Orally Administered Diclofenac or ADX-246



# ADX-246 Demonstrated Statistically Significant Activity in the Carrageenan Inflammatory Pain Model

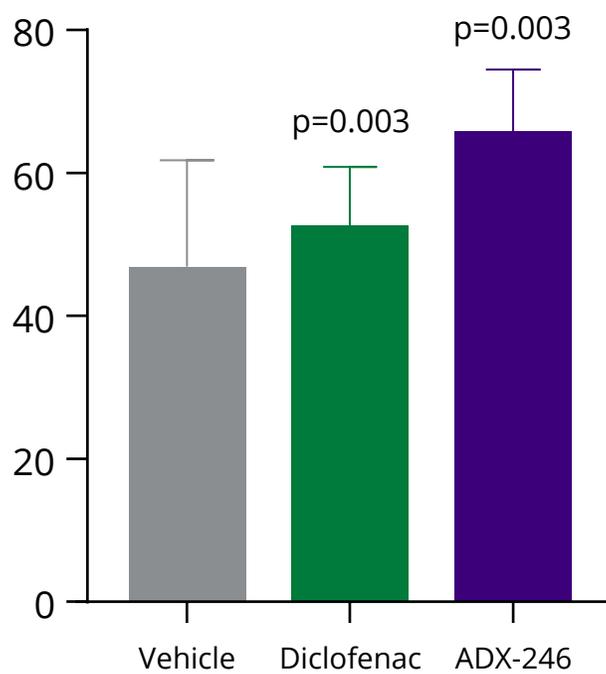
## Mechanical Pain Tolerance

AUC (grams\*hour)



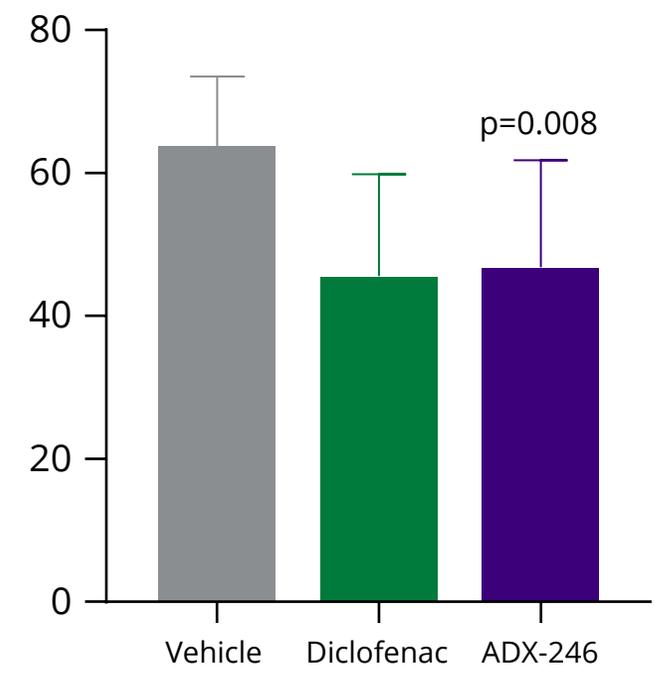
## Thermal Pain Tolerance

AUC (seconds\*hour)



## Swelling

AUC (% increase\*hour)

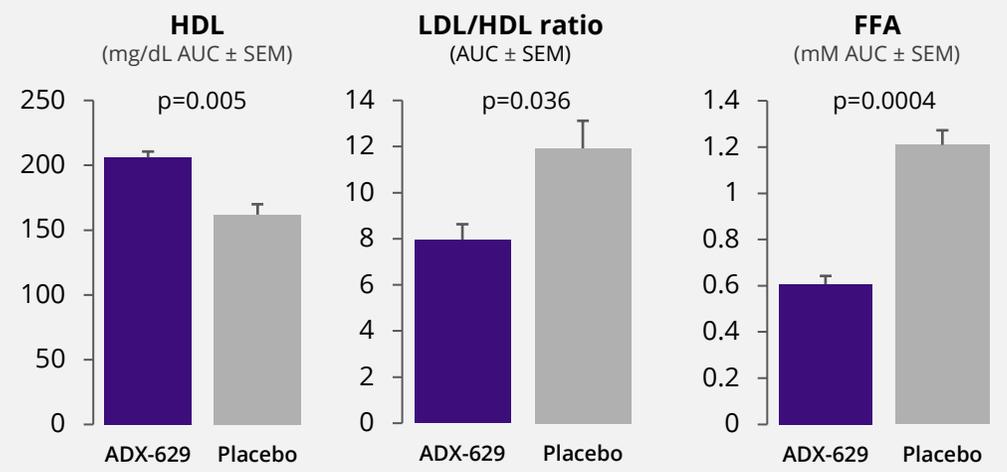




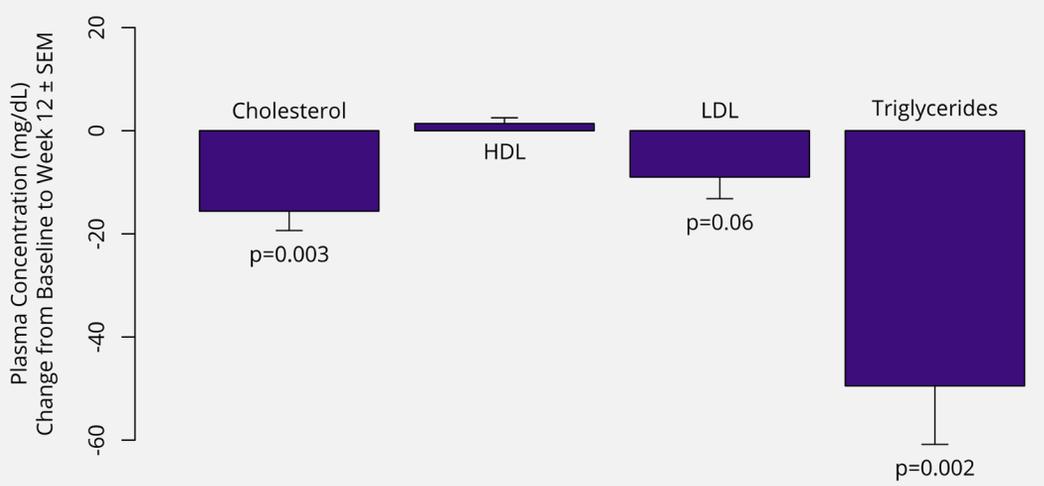
# Lipogenesis Modulation

# Statistically Significant Changes Observed in Lipid Profiles in Multiple Clinical Trials with RASP-Sequestering Molecule ADX-629

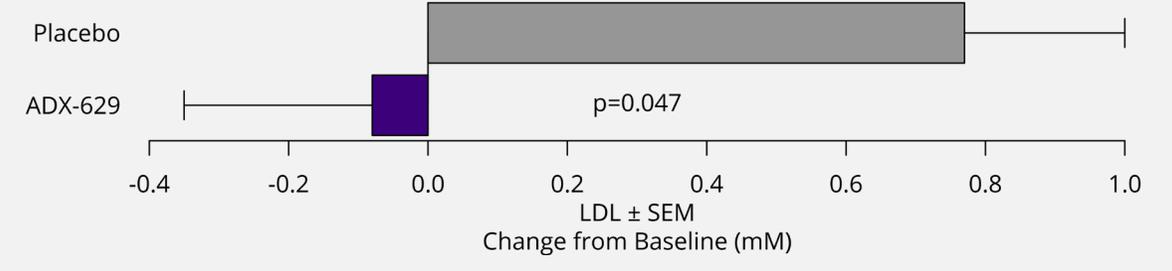
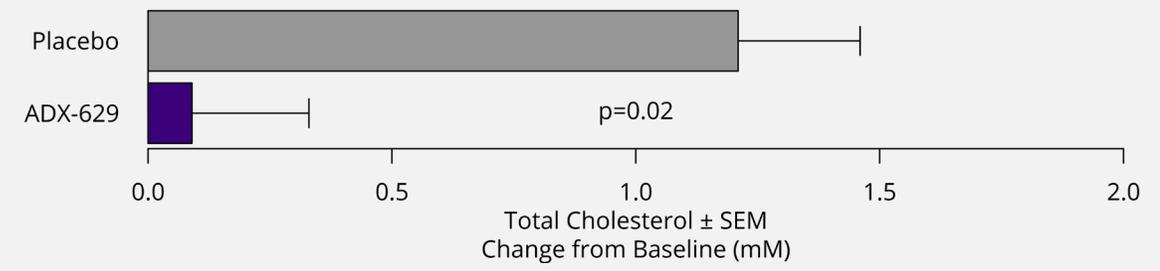
## Phase 1 Clinical Trial



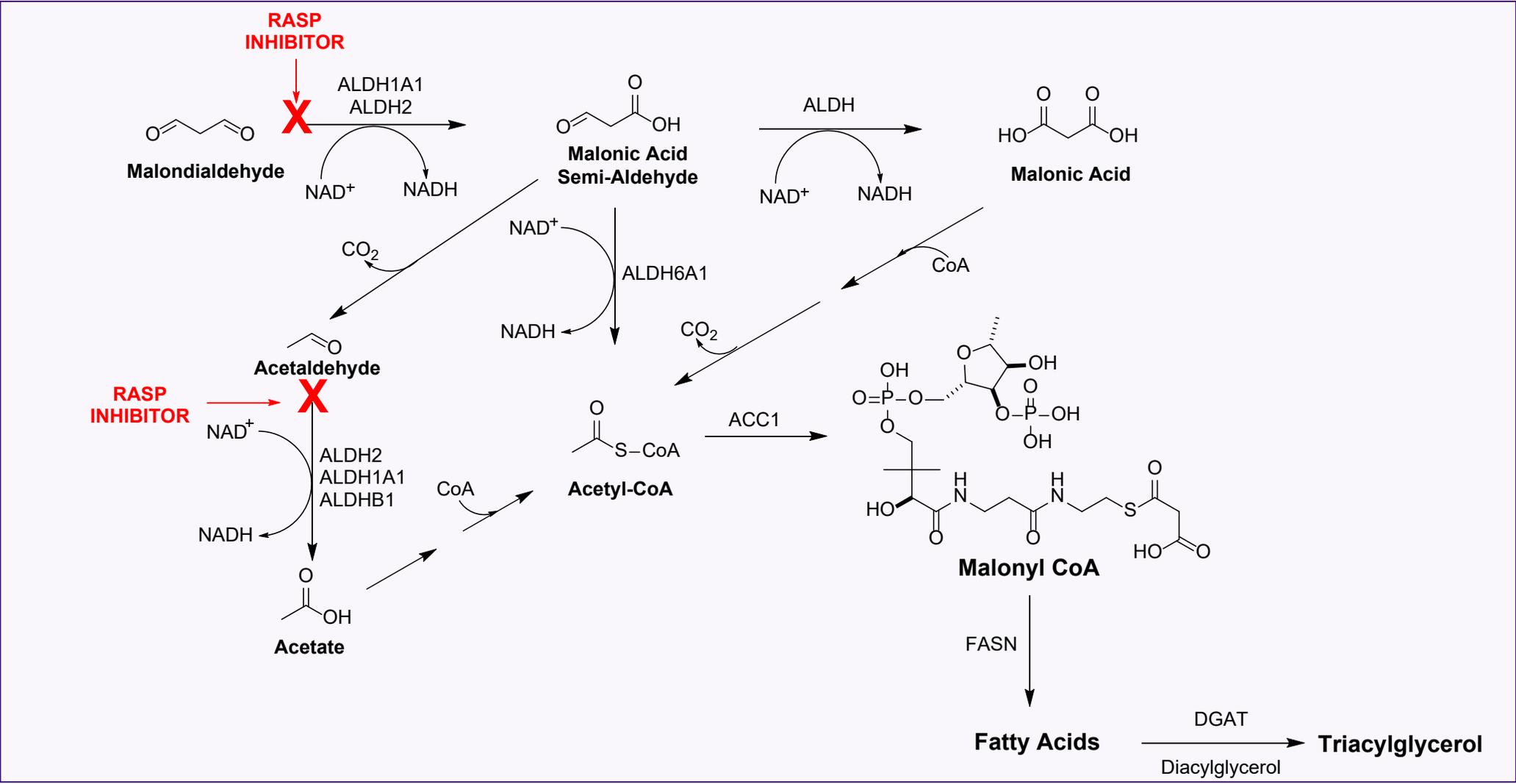
## Phase 2 Psoriasis Clinical Trial



## Phase 1/2 Ethanol Toxicity Clinical Trial

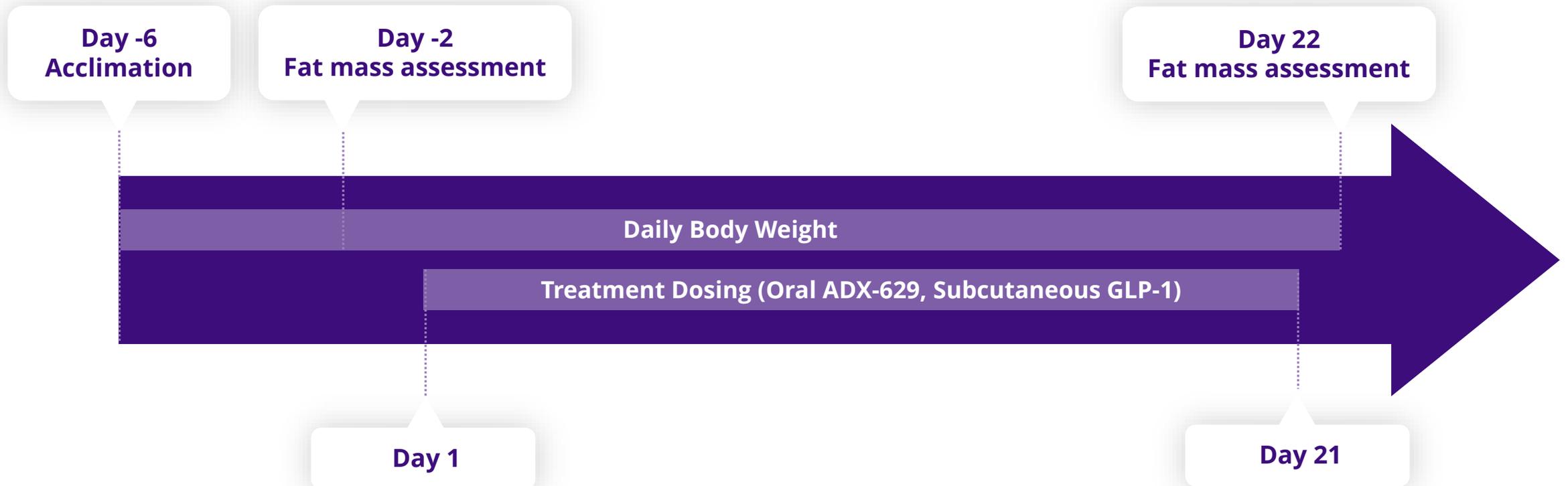


# RASP May Potentiate Triglyceride Synthesis

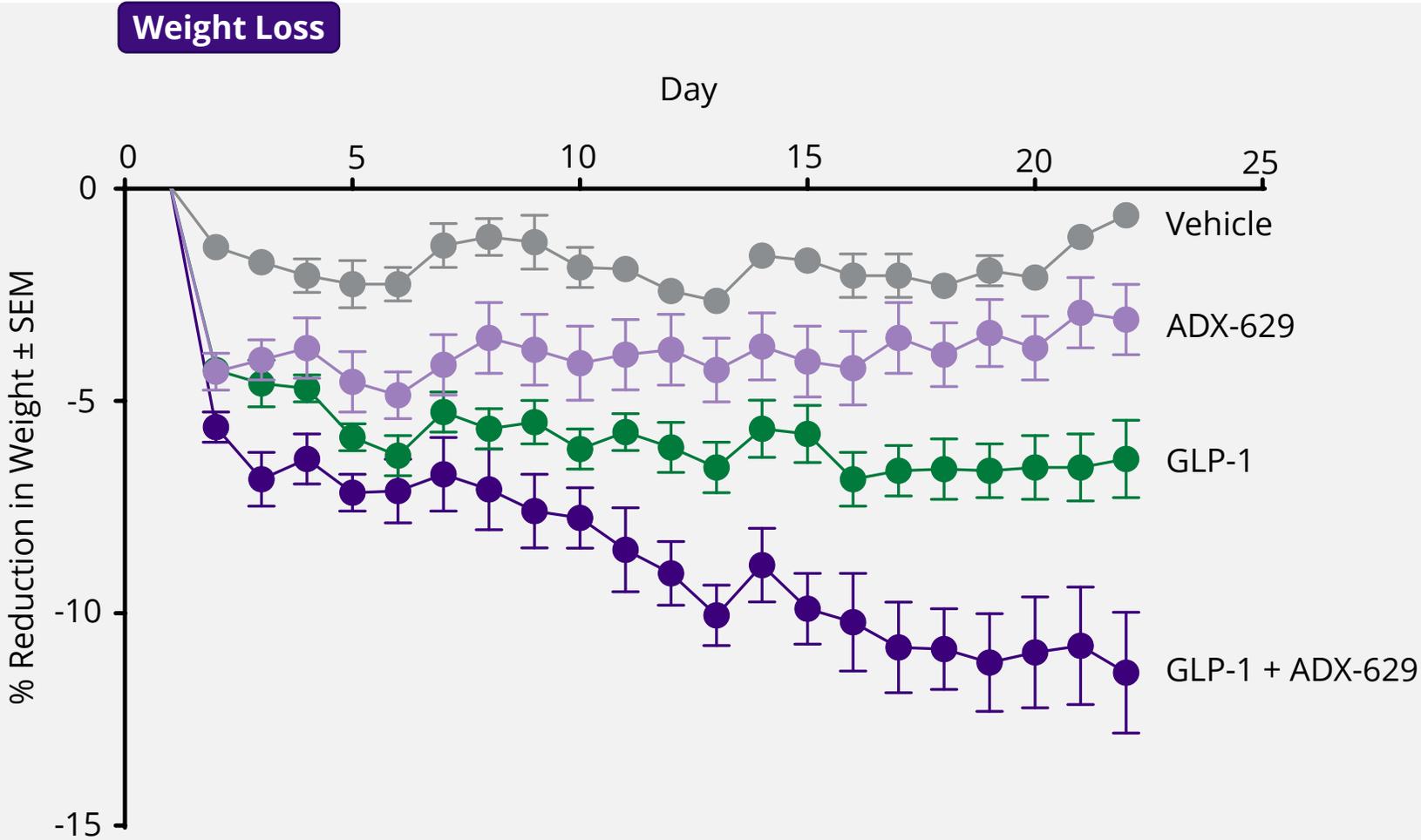


ALDH = aldehyde dehydrogenase. DGAT = diglyceride acyl transferase. ACC1 = acetyl coenzyme A carboxylase. FASN = fatty acid synthase. CoA = coenzyme A. NAD = nicotinamide adenine dinucleotide.

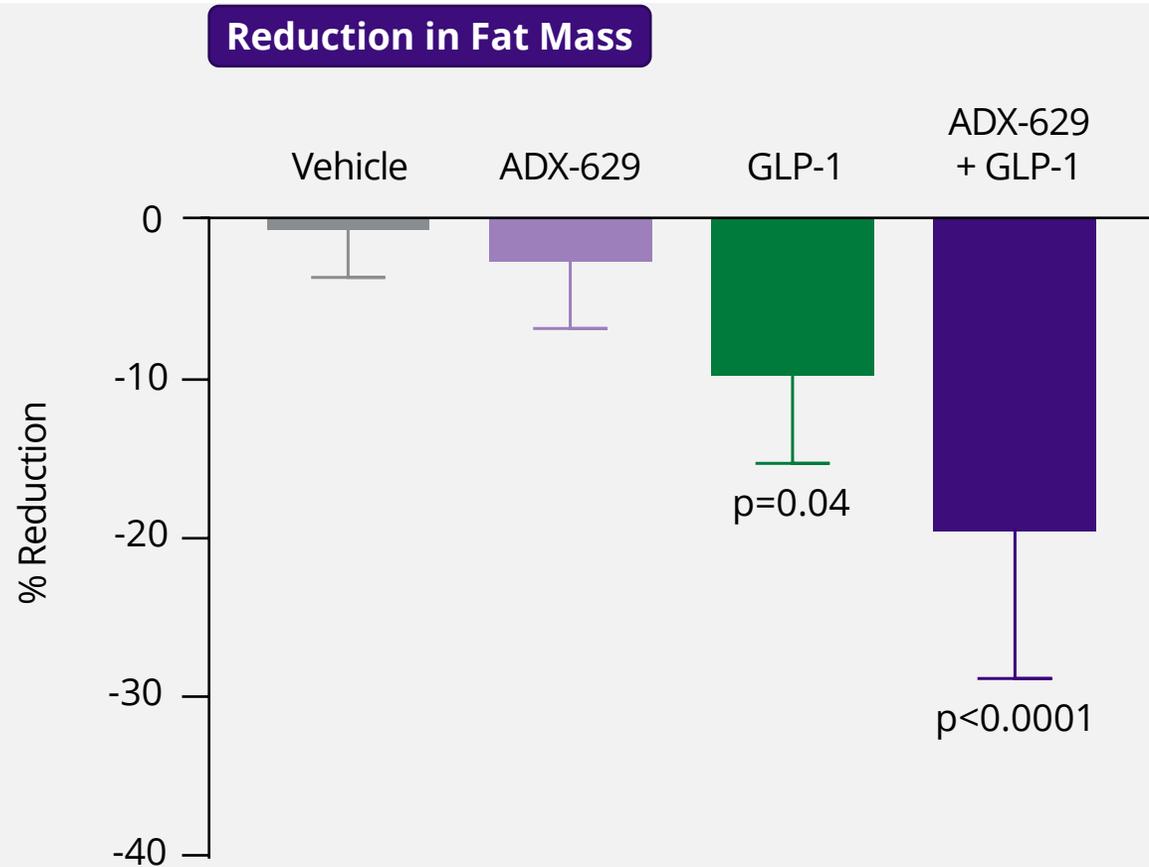
# High-Fat Diet-Induced Obesity Model Allows for Assessment of Weight Loss and Body Composition



# Treatment with Oral ADX-629 Enhanced GLP-1 Weight Loss in Preclinical Model of Obesity



# Treatment with Oral ADX-629 Enhanced GLP-1 Fat Mass Loss in Preclinical Model of Obesity





Questions



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**Ramiro S. Maldonado, M.D., Assistant Professor of Ophthalmology, Duke University**

# Retinitis Pigmentosa: An Overview

# Retinitis Pigmentosa: An Overview

**Ramiro Maldonado, MD**



**Duke Ophthalmology**

Duke University School of Medicine

**1<sup>st</sup> intra-op  
OCT**



**1<sup>st</sup> Handheld  
OCT**



 **Duke Ophthalmology**  
Duke University School of Medicine

**DPROC**  
Duke Pediatric Retina & Optic Nerve

 **Duke Center for Ophthalmic Genetics**  
Duke University School of Medicine



 **Duke Eye Center**

 **NIH** National Eye Institute  
Research Today...Vision Tomorrow

 **University of  
Kentucky**

# HELLO!

**Ramiro Maldonado, MD**  
**Co-Director Pediatric Retina**  
**Retina Specialist**  
**Ophthalmic Geneticist**

# Financial disclosures:

- ProQR Therapeutics Consultant
- PYC Therapeutics Consultant
- Aldeyra Therapeutics Consultant
- Duke Eye Reading Center Consultant



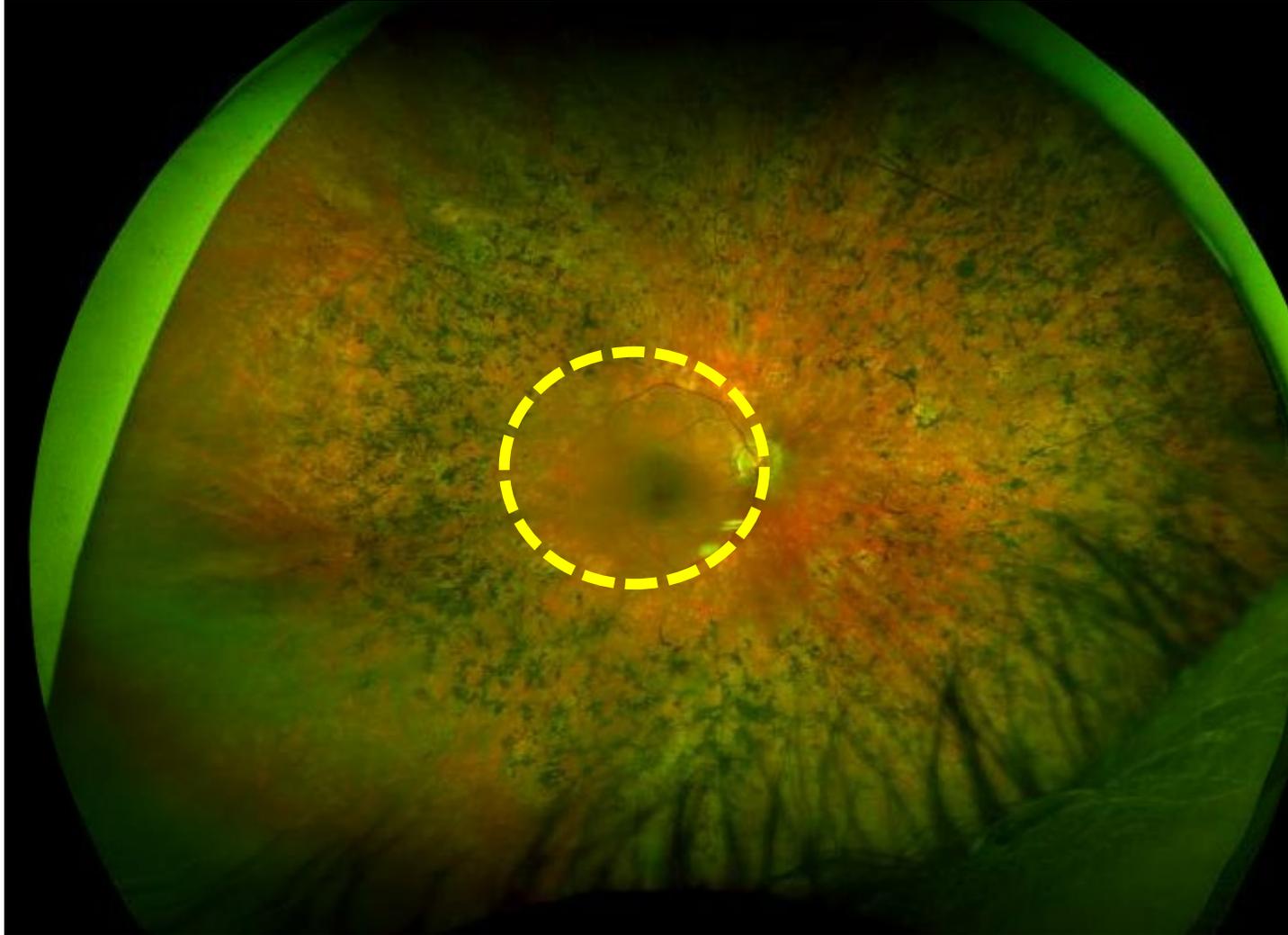
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**Let me show you a  
patient problem....**

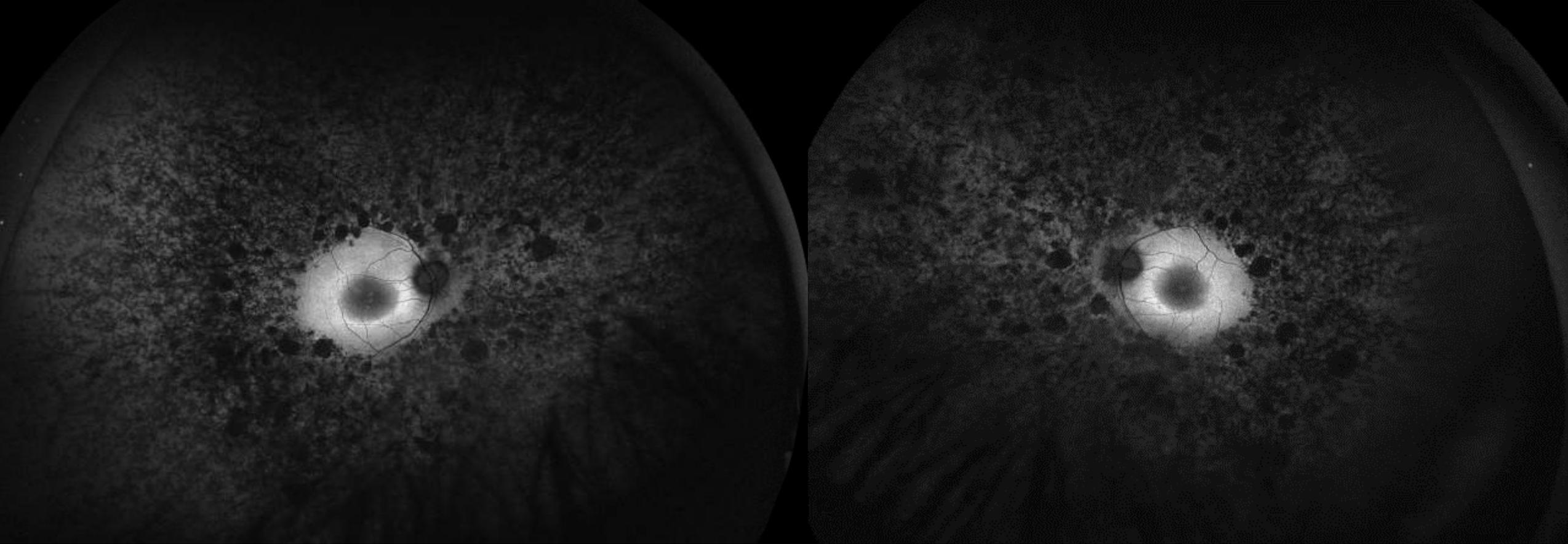


**42 y/o in the  
prime of his life...**

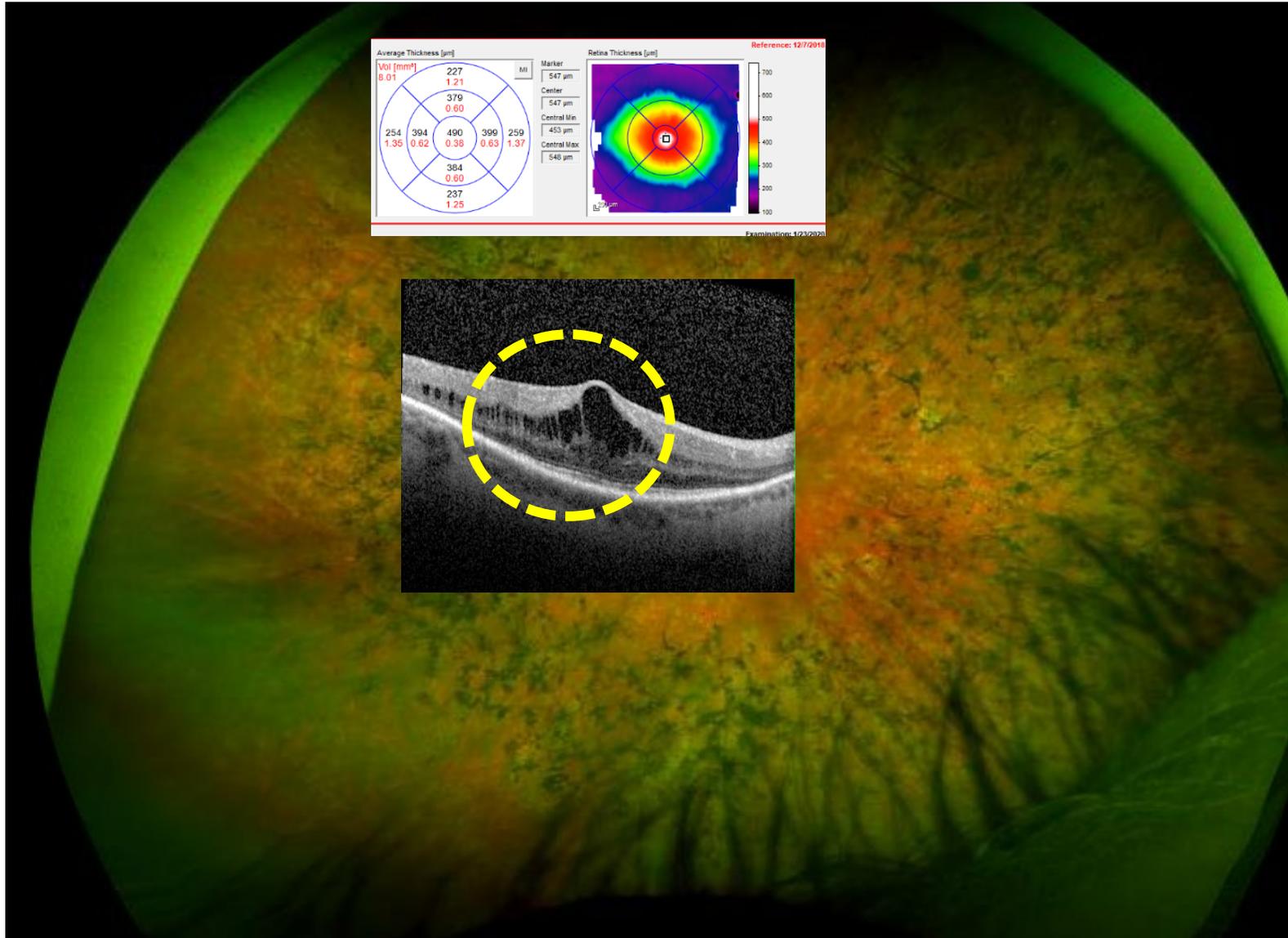
**Diagnosed with  
Retinitis  
Pigmentosa...**



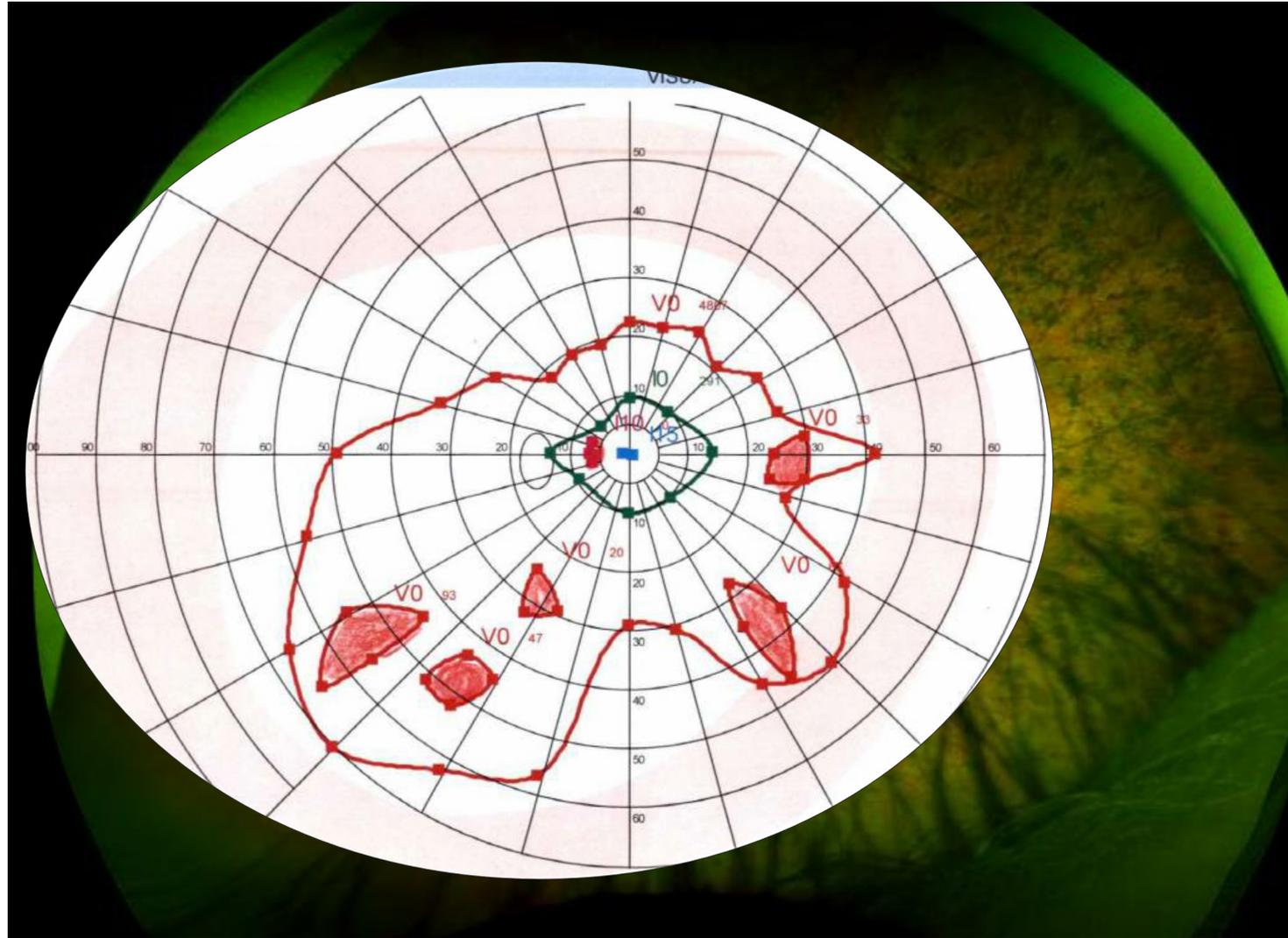
# Significant extent of retinal degeneration



# Living Histology



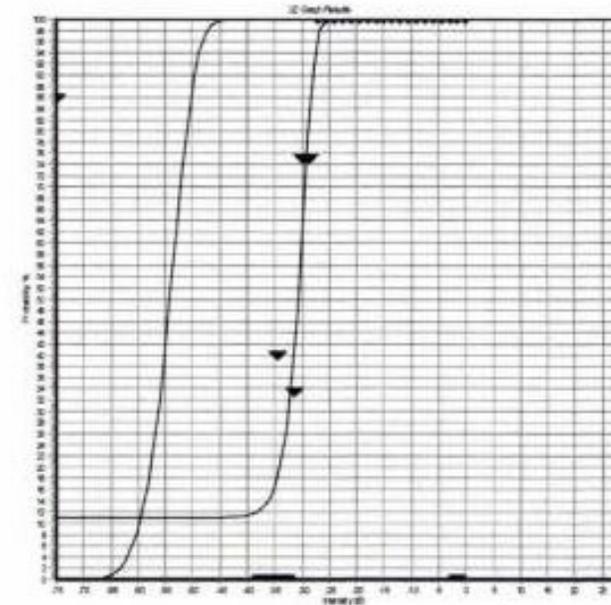
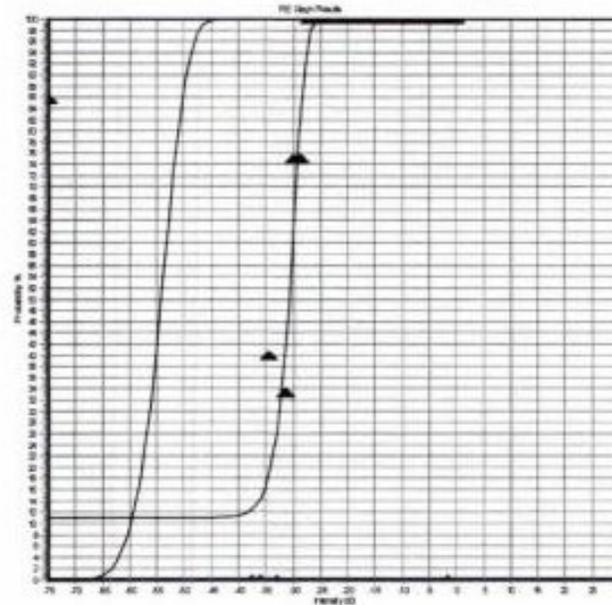
# Constricted visual fields



# Minimum light stimulus perceived (FST test)

Average Results Table												
#	Color	Eye	dB	EB%	EM%	TO	n	Qty	Date	P0	Y	K
3	White	LE	-31.0	0	0	0	2	1	1/23/2020	0	45.032	16.053
3	White	RE	-31.0	0	0	0	2	1	1/23/2020	0	45.032	16.053

Individual Results Table													
#	Color	Eye	dB	EB%	EM%	TO	n	Qty	Date	P0	Y	K	Time
1	White	LE	-54.2	0	0	0	3	1	1/23/2020	0	22.118	6.0509	00:00:15
2	White	LE	-30.4	14	45	0	56	2	1/23/2020	0.1107	45.385	21.676	00:04:37
1	White	RE	-54.2	0	0	0	3	1	1/23/2020	0	22.118	6.0509	00:00:15
2	White	RE	-30.4	14	45	0	56	2	1/23/2020	0.1107	45.385	21.676	00:04:37



# IRDs

Inherited Retinal Diseases



The big picture



6,800,000

People in the world with IRDs



300,000

People in the USA with IRDs



6,800,000 people

WORLDWIDE

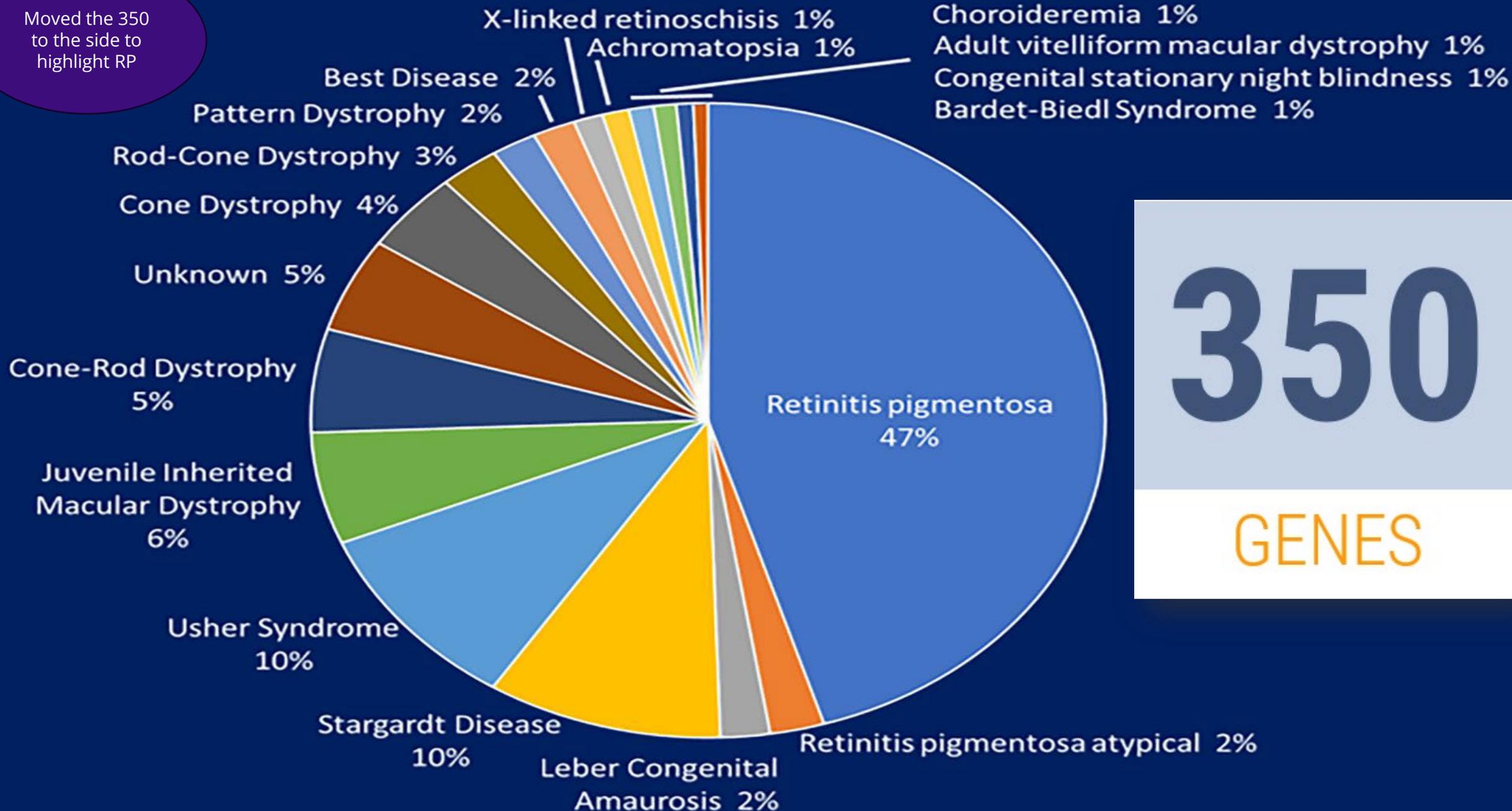
300,000 people

In the US

1

FDA approved therapy

Moved the 350 to the side to highlight RP



350  
GENES



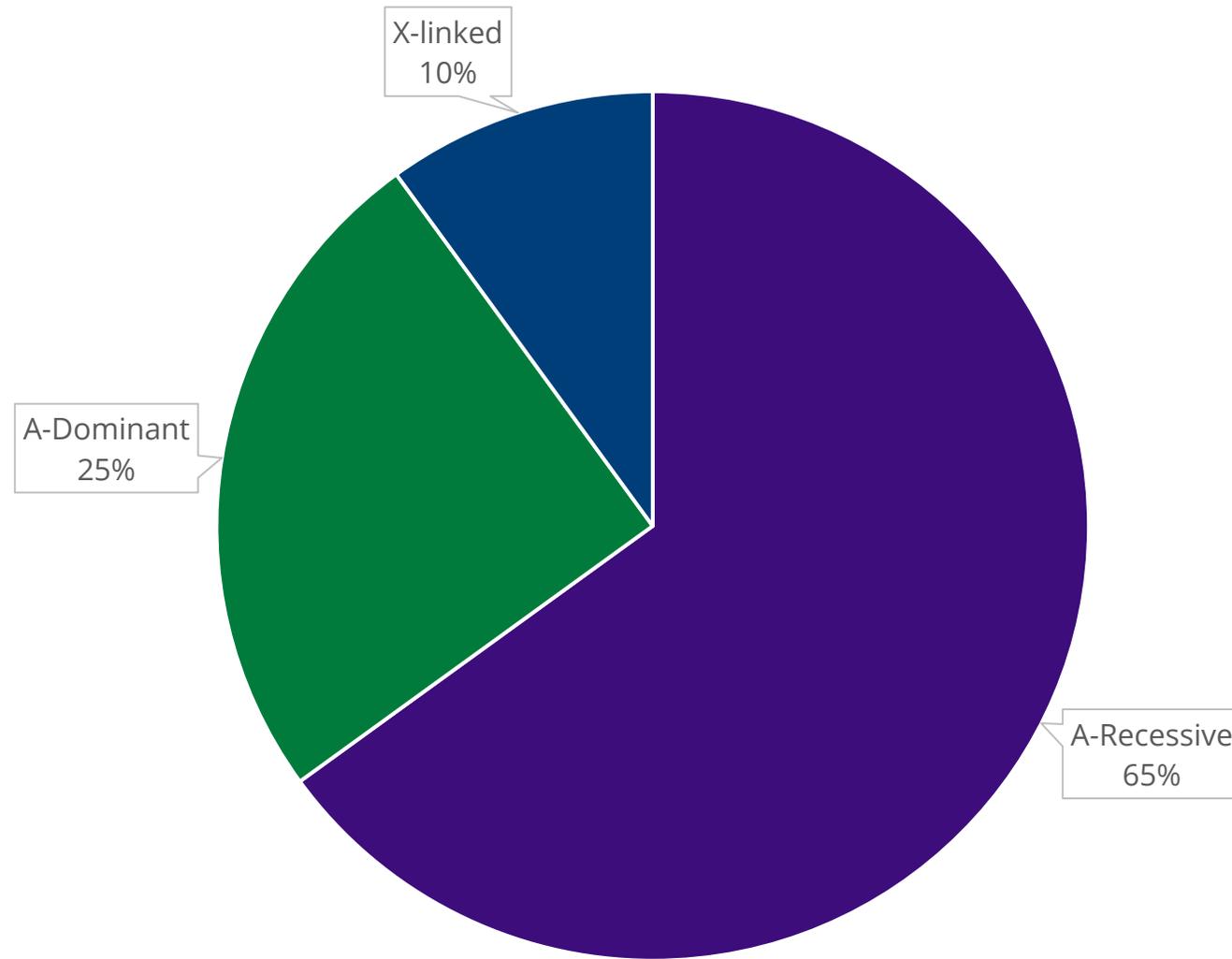
350

IRD-GENES

60

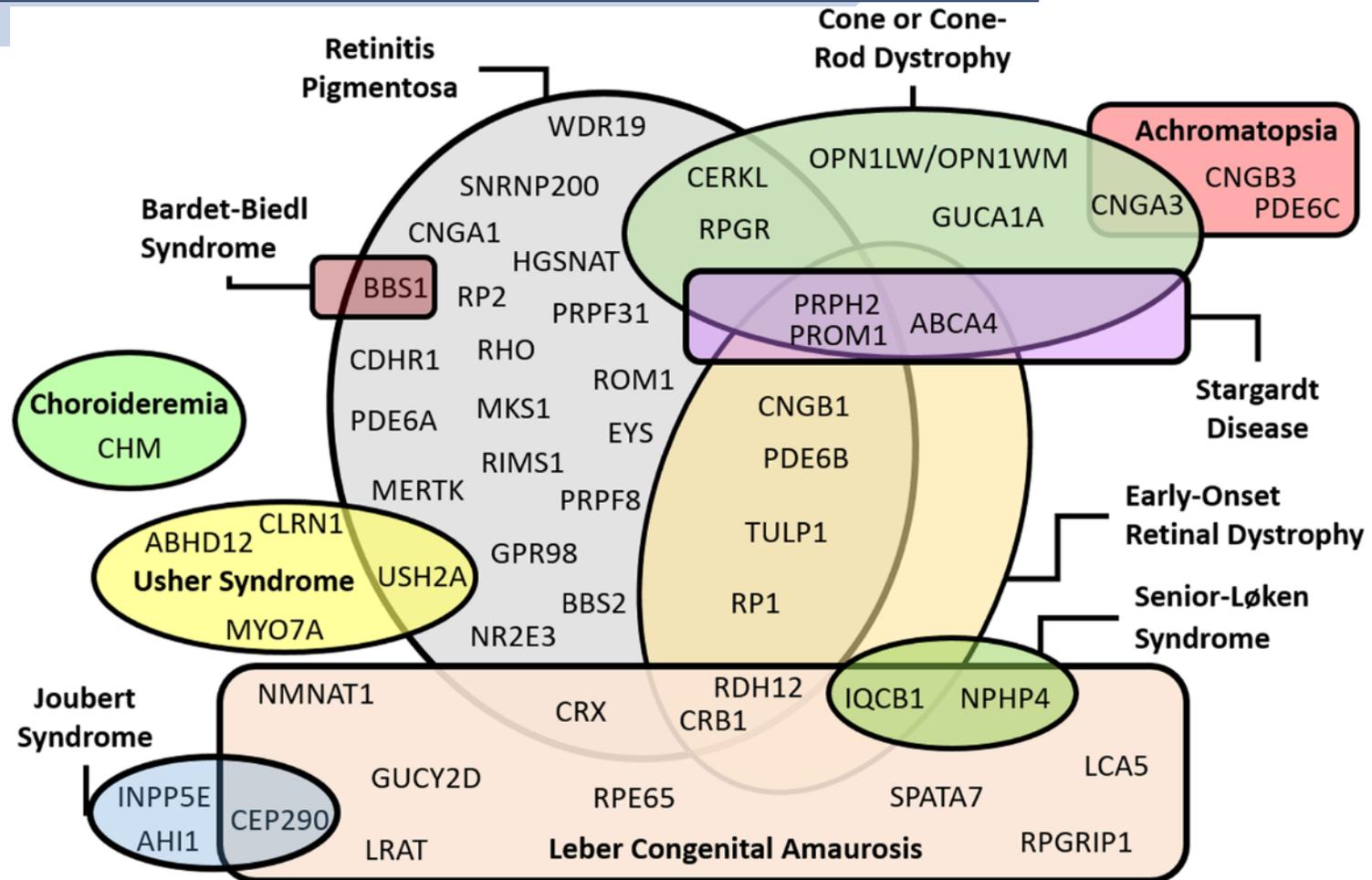
RP-GENES

60  
RP-GENES



# Genetic heterogeneity

One disease can be caused by multiple genes





Genetics is  
changing the  
naming of diseases



Research Building



Clinical Building



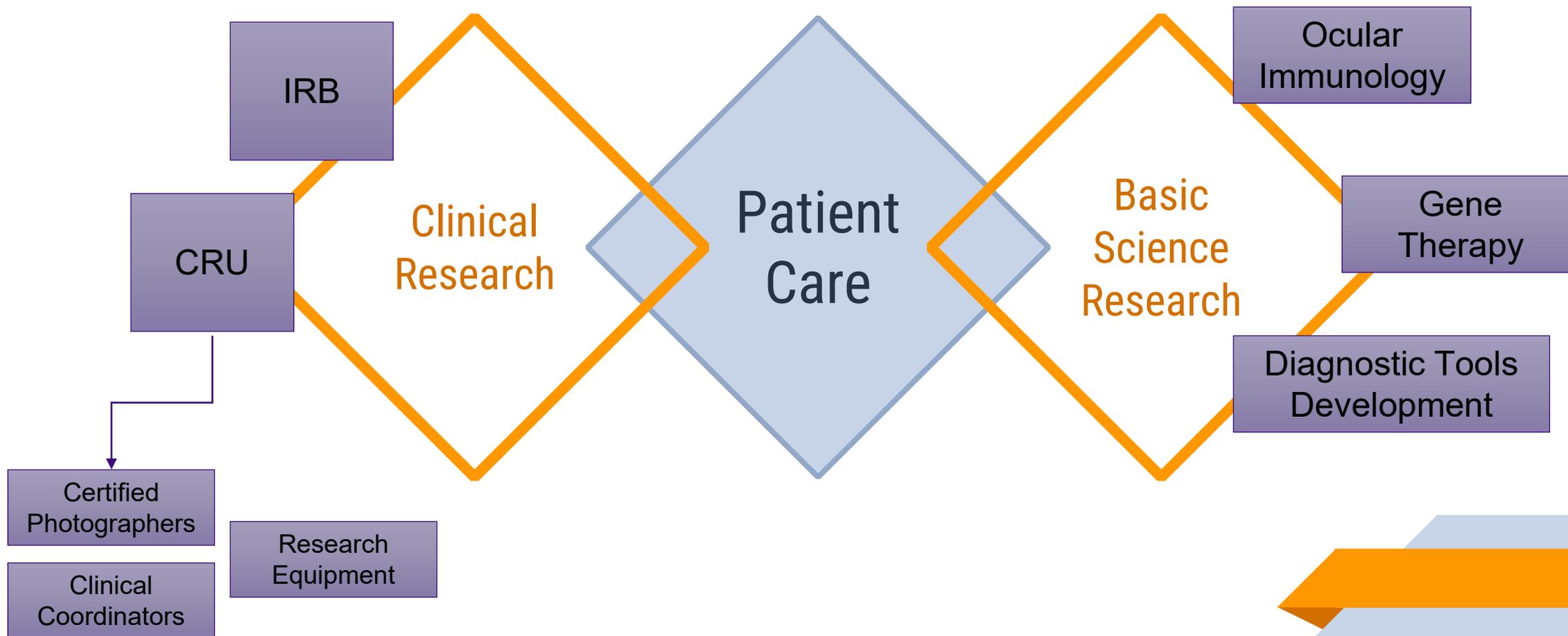


5,200 patients / year

Ophthalmic Genetics Service



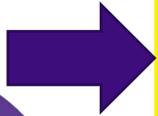
# Clinical and Research integration



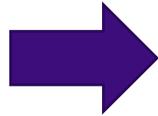
# The patient's journey



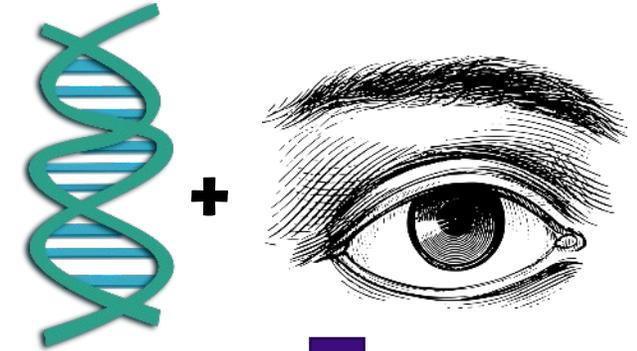
**Patient  
with IRD**

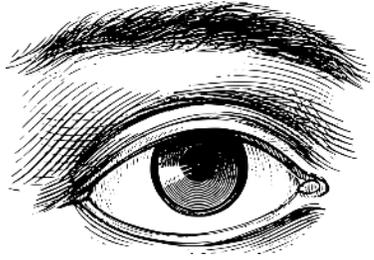


**Optometrist  
Pediatric Oph  
Retina Spec**



**Eye  
Genetics  
Service**





## Comprehensive Hx

**Non-Syndromic**

**Syndromic**

**Rod-specific**

**Cone-Specific**

**Optic Nerve**

## Pedigree

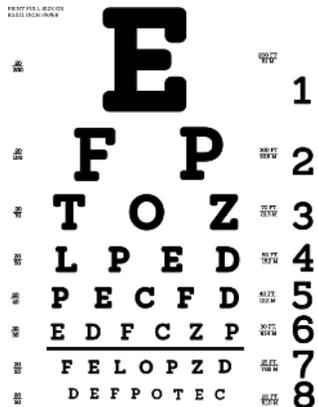
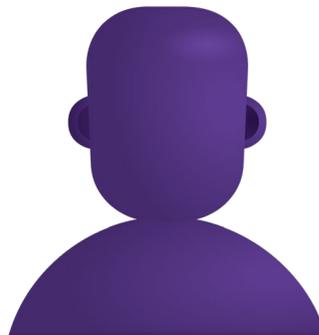
**A Dominant**

**A Recessive**

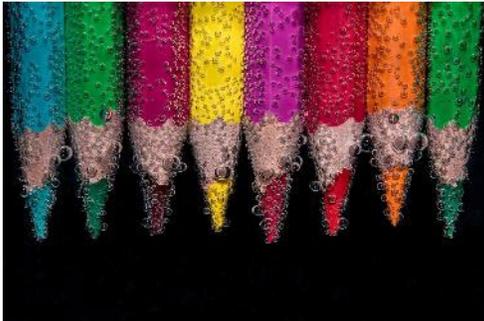
**X-linked**

**Mitochondrial**

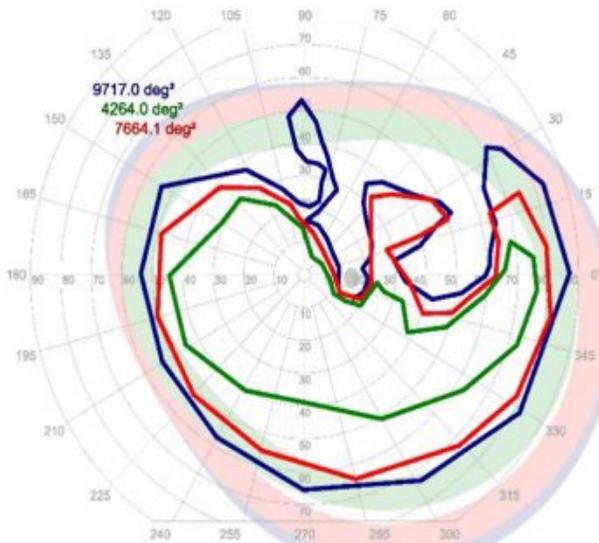
## Visual Acuity



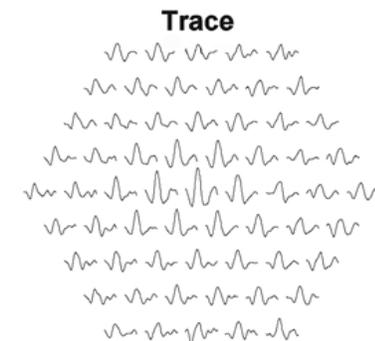
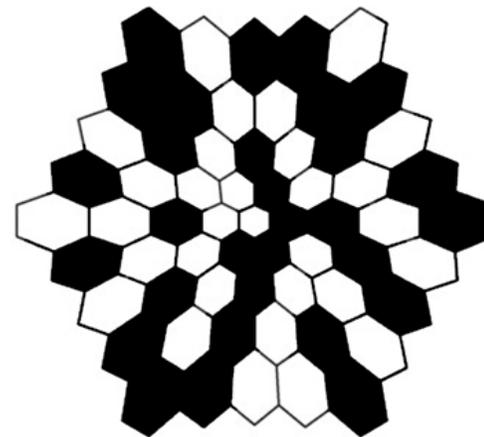
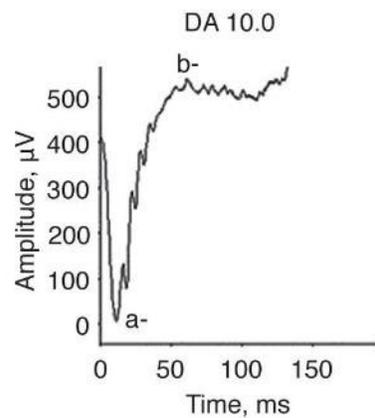
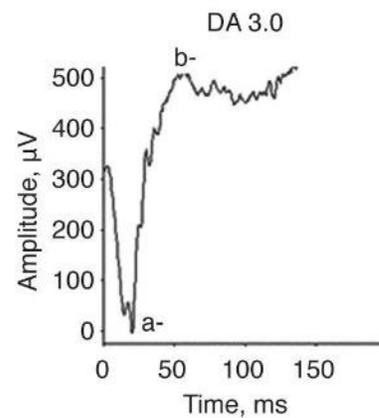
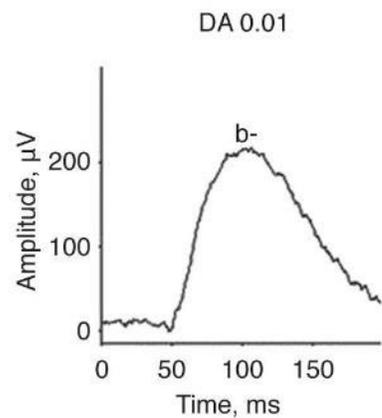
## Color vision



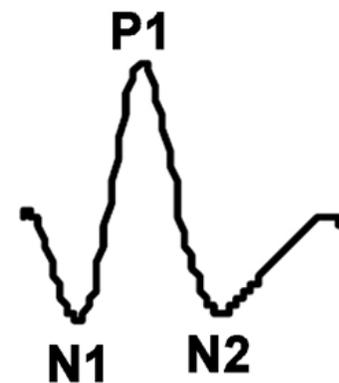
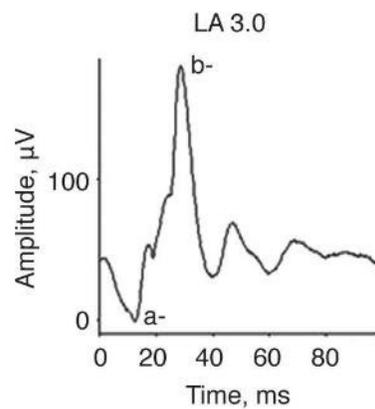
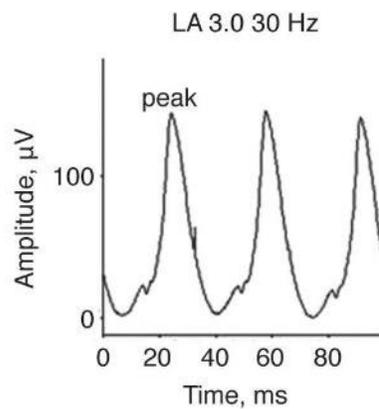
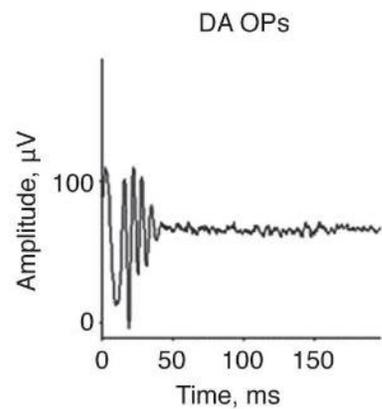
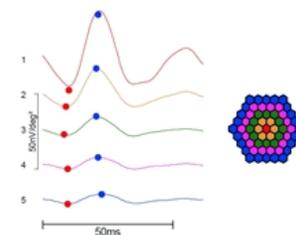
## Visual Field



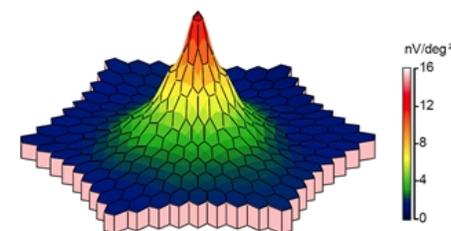
# Objective functional outcomes

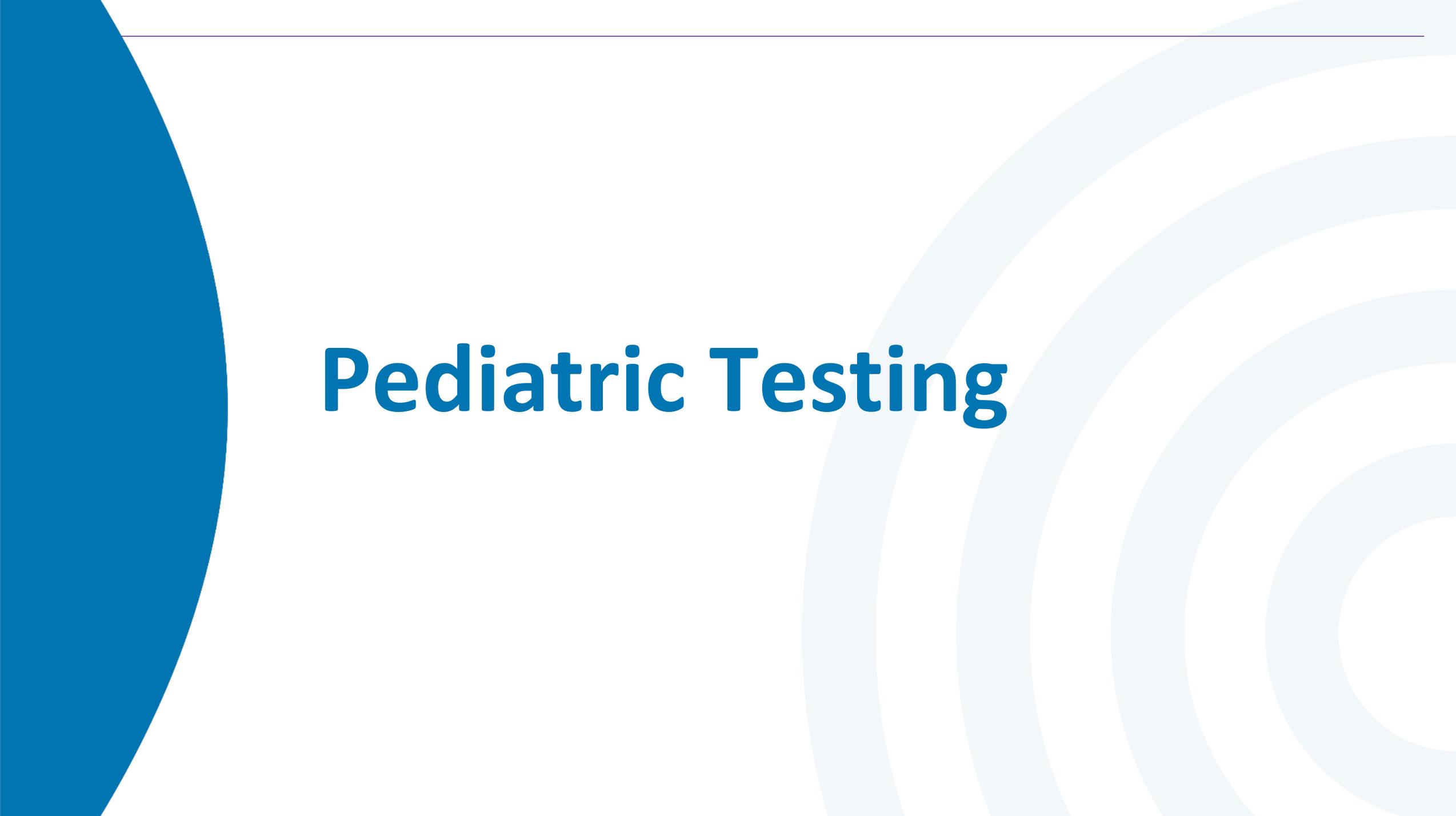


Group averages



3D Topography

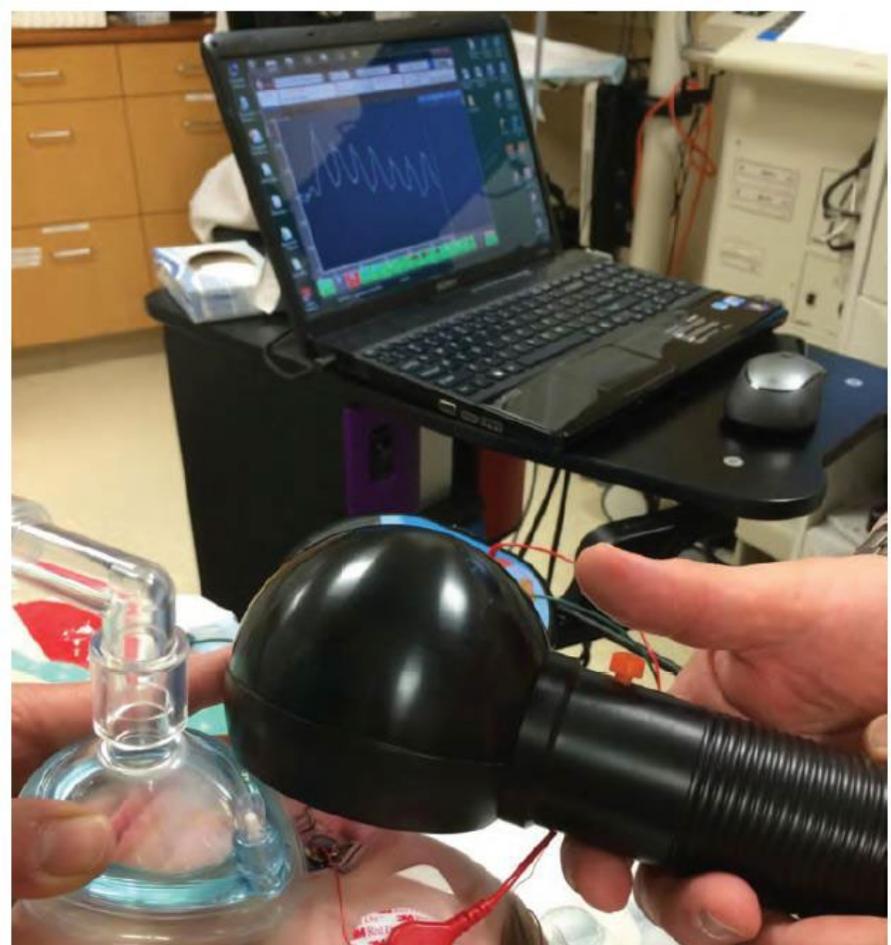




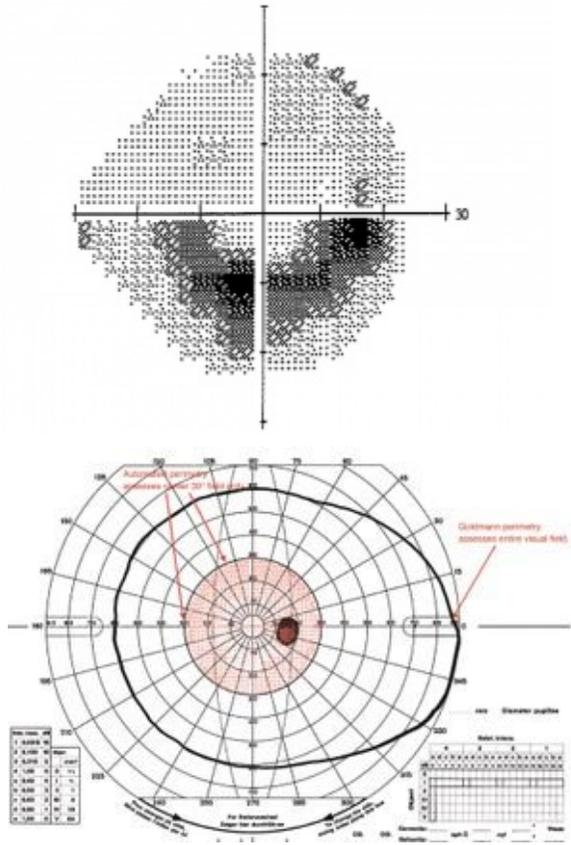
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# Pediatric Testing

# Hand Held ERG and ERG under anesthesia



# Perimetry

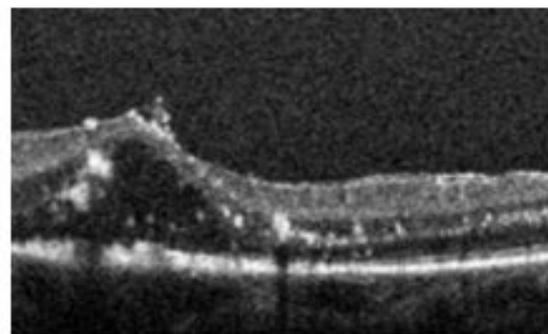
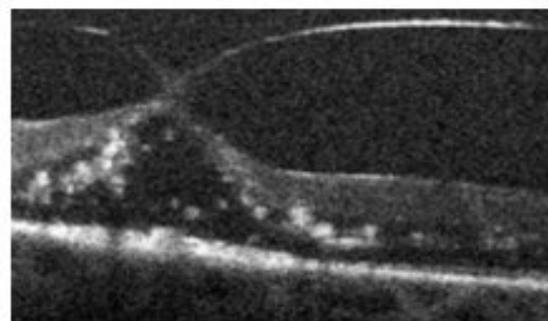


# OCT imaging in Surgery

- Portable system
- Pause to image



Joseph  
Izatt



- Dayani PN, Maldonado R, Farsiu S, Toth CA Retina, 2009
- Scott AW, Farsiu S, Enyedi LB, Wallace DK, Toth CA. AJO, 2009
- Ehlers JP, Kernstine K, Farsiu S, Sarin N, Maldonado R, Toth CA. Arch Ophthalmol. 2011



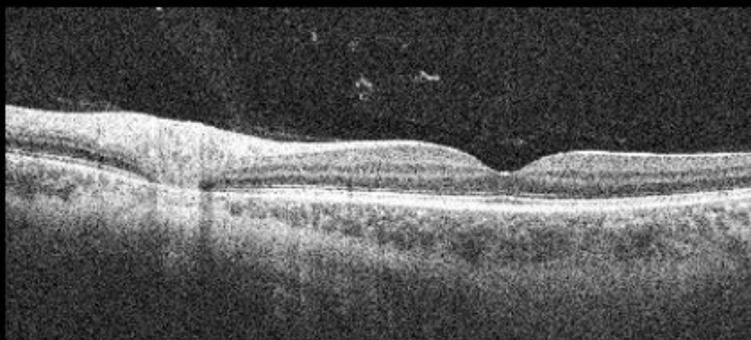
# Faster OCT imaging in BabySTEPS2



**400 kHz  
Swept Source  
OCT**



OCT imaging  
NOT a photo



*Viehland et al BOE 2019*

*Mangalesh S Ophthalmology Retina 2020*

# VIRTUAL REALITY TEST

**MOST<sup>VR</sup>**

**State-of-the-art Mobility Testing for  
Inherited Retinal Diseases**



# Genetic Testing is now Standard of Care





For a long time...

There was **NO HOPE**  
for patients with IRDs



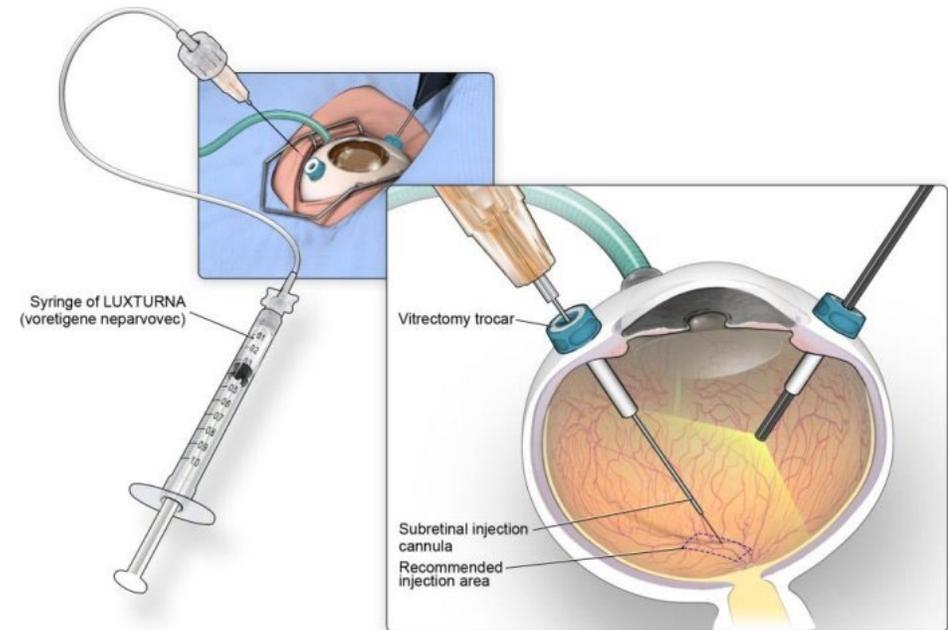
# FIRST IN HUMAN

BEFORE THE BREAKTHROUGH  
COMES THE TRIAL

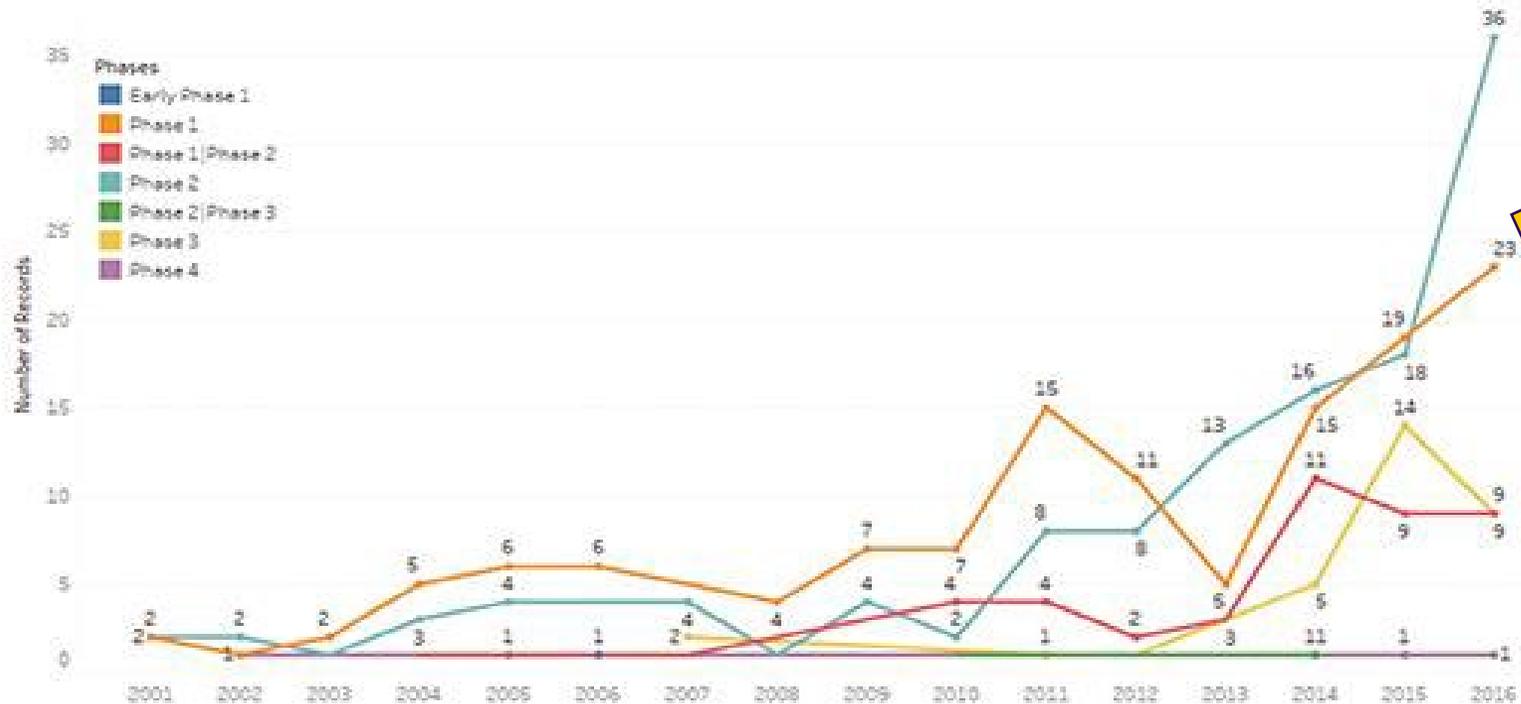


# Gene Therapy

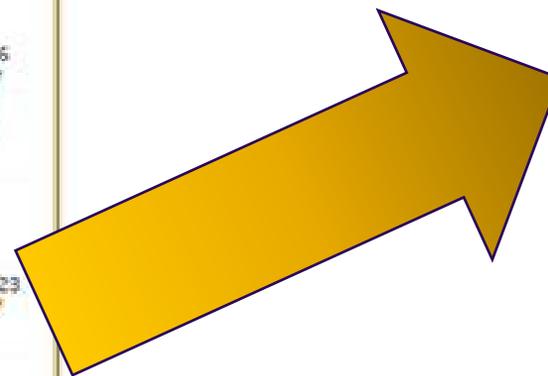
# There is an FDA approved Gene therapy



## Number of Gene Therapy Clinical Trial Initiations Per Year, by Phase



**The industry-wide gene therapy pipeline shows exponential growth.**



A landscape featuring a vibrant green rolling hill in the foreground. A single, full-canopied tree stands on the crest of the hill. The sky is filled with dramatic, dark grey clouds, with a bright light source breaking through in the center, creating a lens flare effect. A flock of birds is visible in flight against the lighter part of the sky. The overall mood is one of hope and renewal.

We do have treatments for  
IRDs!

**It's a new era**

# Gene therapy is a reality but...

Can we miss the boat?

How many studies are failing?

Is there a risk to lose momentum?



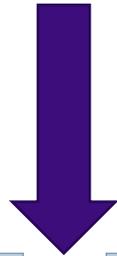
# Early detection means

Treatment success

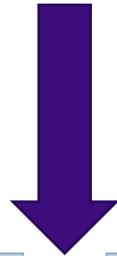
Do we intervene here...



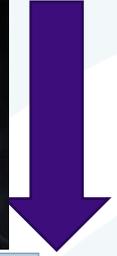
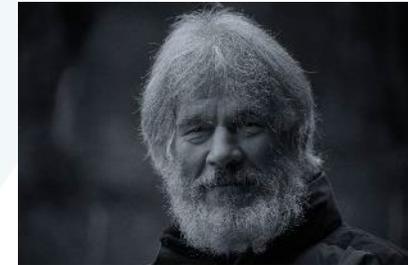
LCA



EO-RCD



RCD



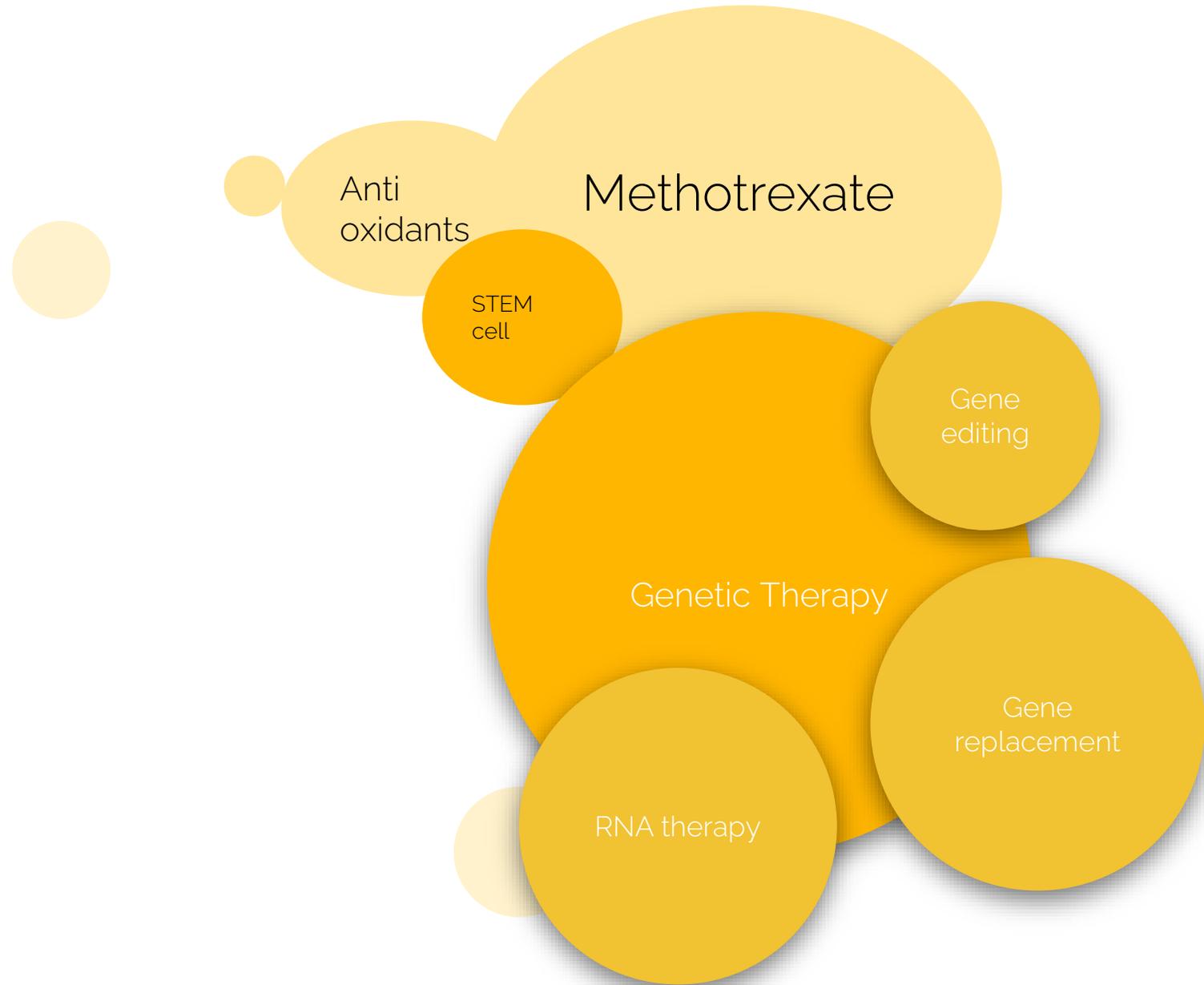
Late-RCD



Or here...



# There are multiple proposed Therapies



# Gene-dependent ← → Gene-INDEPENDENT



RPE65



CEP290



## Therapies

## Anti-oxidants



Methotrexate



CVF



Opto-G



SC

RPGR

ProQR

CEP290

ABCA4

RHO

USH2A

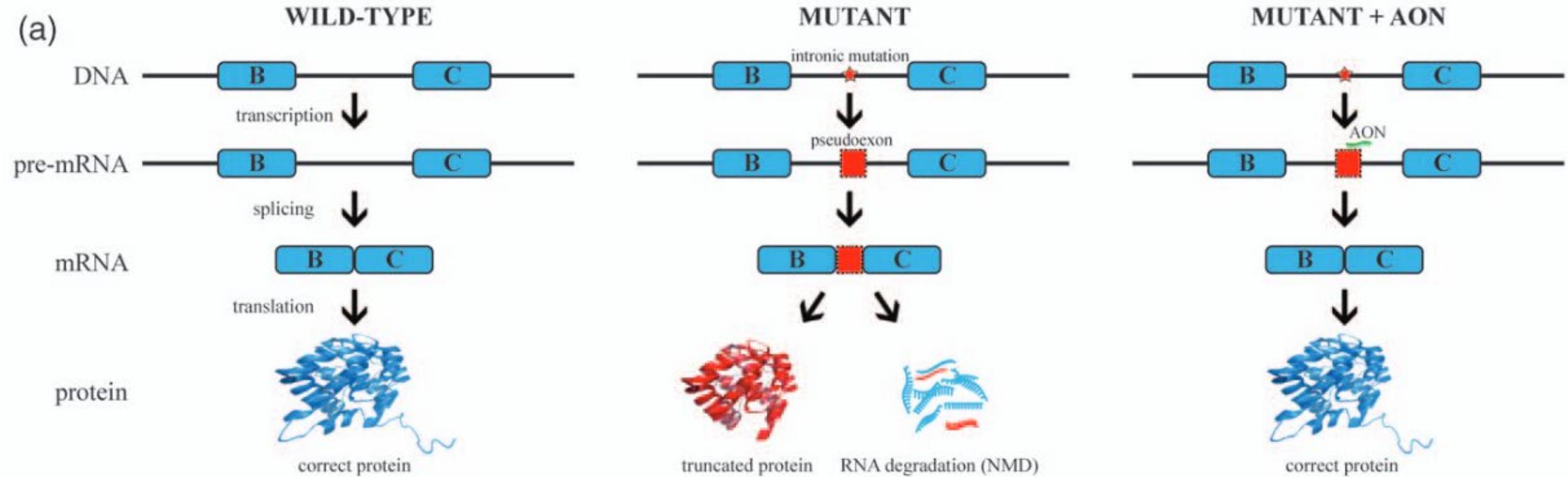


# Beyond Luxturna

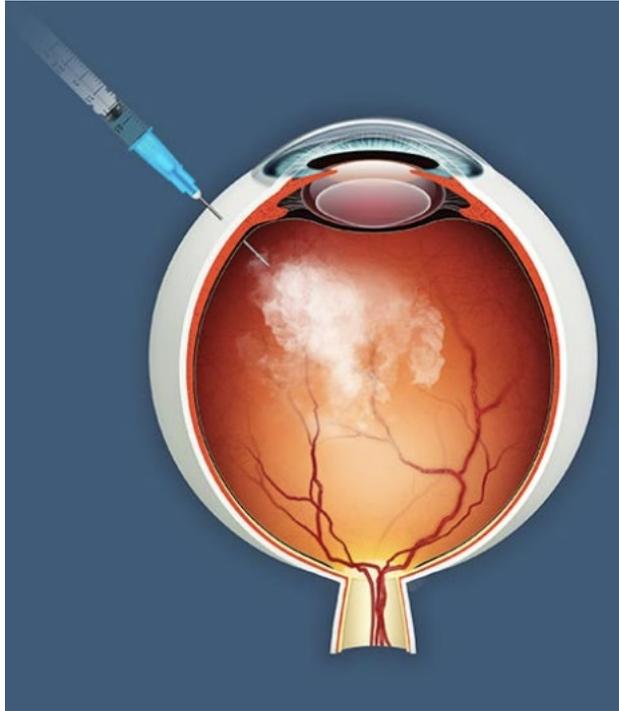
# RPE65

- **RPGR**
- **ABCA4**
- **USH2A**
- **RHO**
- **CEP290**
- **BEST1**

# RNA Therapy



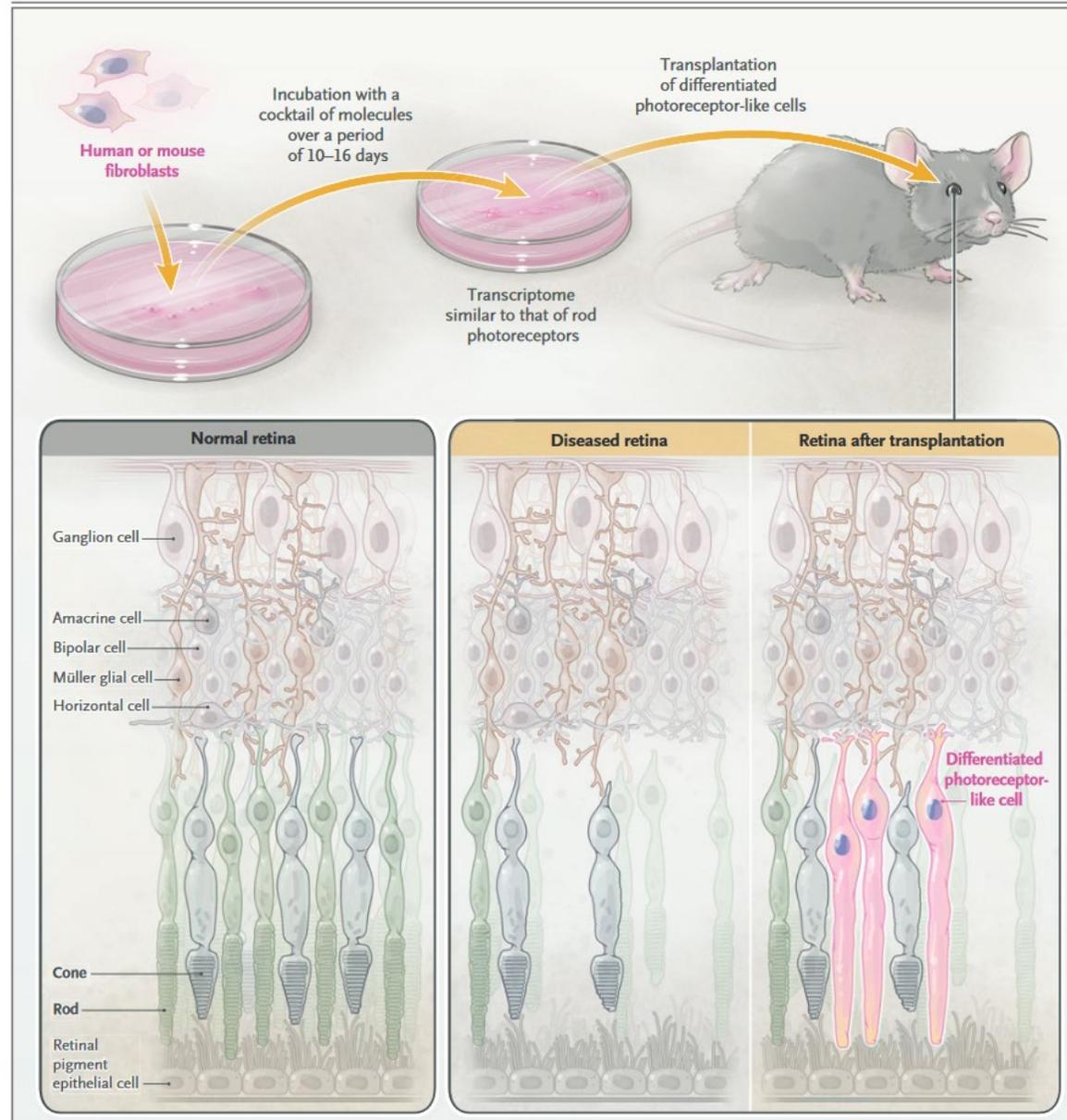
# STEM Cells



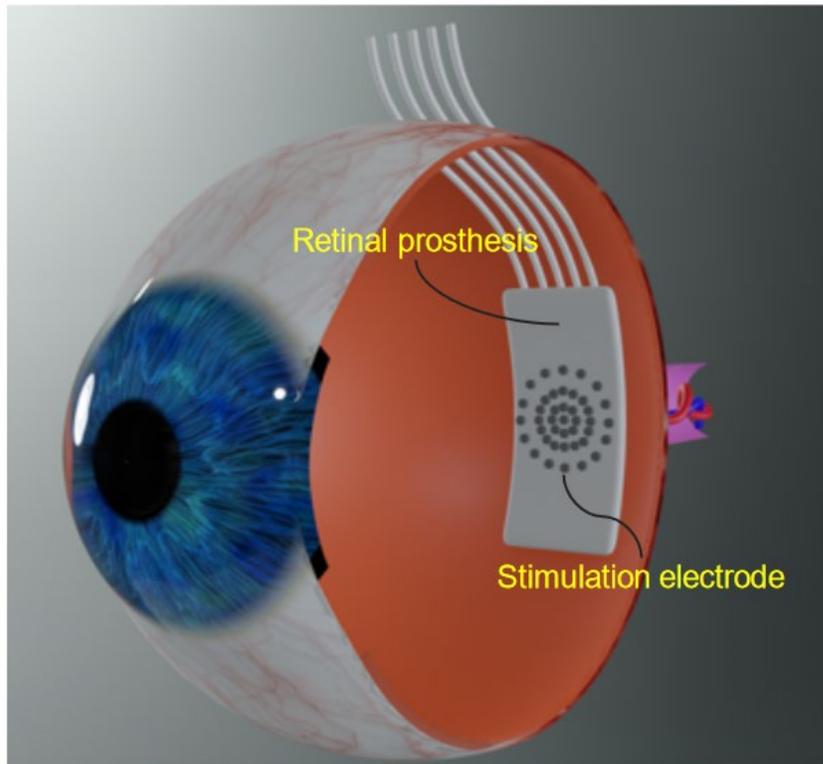
**Intravitreal Injection of Allogeneic Human Retinal Progenitor Cells (hRPC) for Treatment of Retinitis Pigmentosa: A Prospective Randomized Controlled Phase 2b Trial**

[David Liao](#); [David S Boyer](#); [Peter Kaiser](#); [Baruch D Kuppermann](#); [Jeffrey Heier](#); [Mitul Mehta](#); [Anthony Joseph](#); [Rebecca Kammer](#); [Bonnie Mills](#); [Jing Yang](#); [Henry Klassen](#)

# Chemically-Induced Photoreceptors



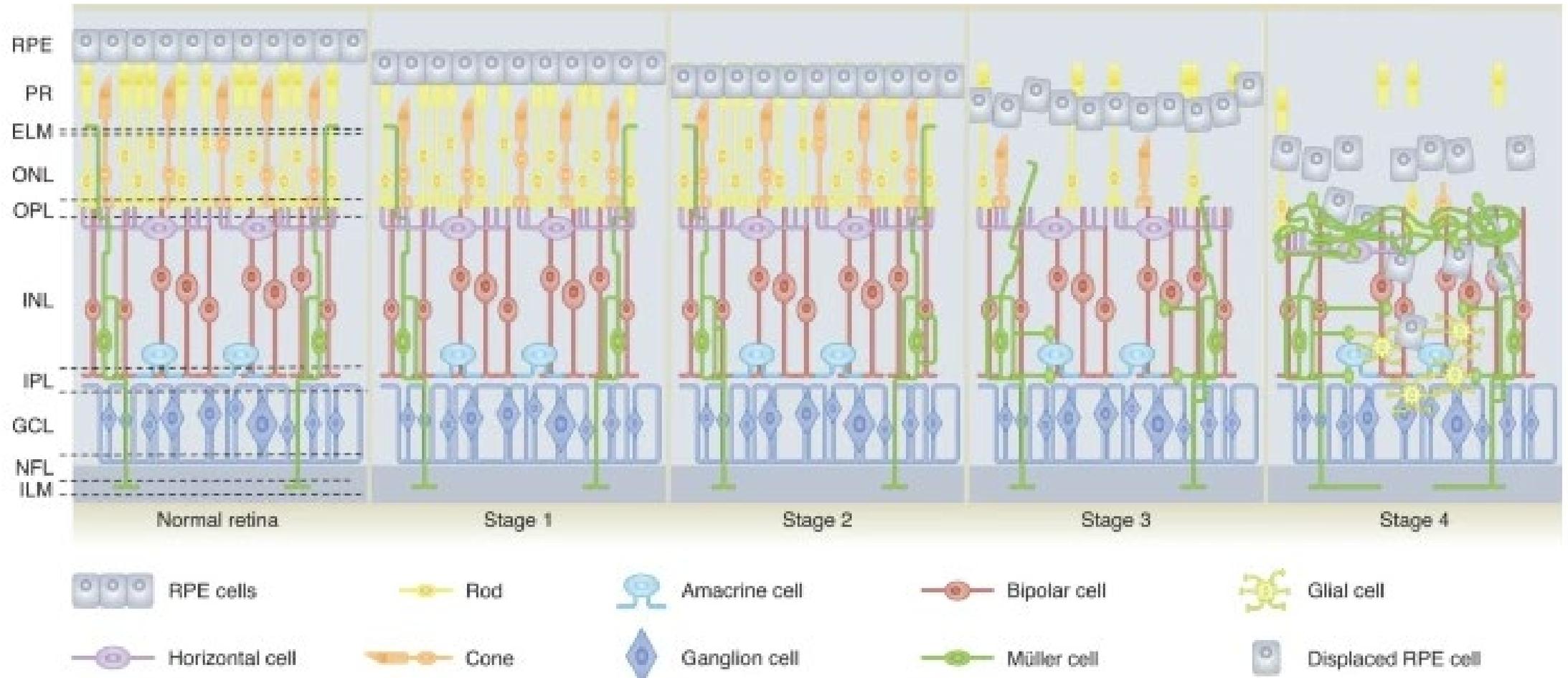
# Retinal Prosthesis



**Implantable metaverse with retinal prostheses and bionic vision processing**

[Ning Xi](#), [Jiaxun Ye](#), [Chao Ping Chen](#), [Qiang Chu](#), [Haiyang Hu](#), [Seak Pang Zou](#)

# A Therapy According to Stage



•Review Article Published: 31 January 2022 **Bioengineering strategies for restoring vision**

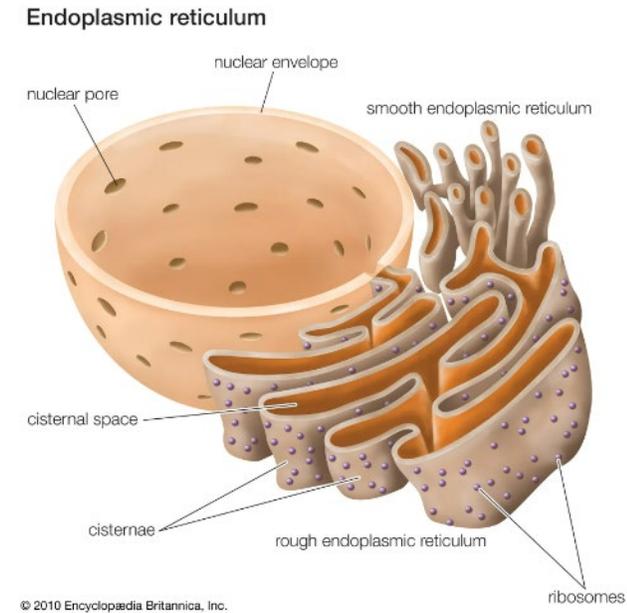
•[Jasmina Cehajic-Kapetanovic](#), [Mandeep S. Singh](#), [Eberhart Zrenner](#) &

•[Robert E. Maclaren](#) *Nature Biomedical Engineering* volume 7, pages387–404 (2023)

## Misfolded Proteins and Retinal Dystrophies

Jonathan H. Lin and Matthew M. LaVail

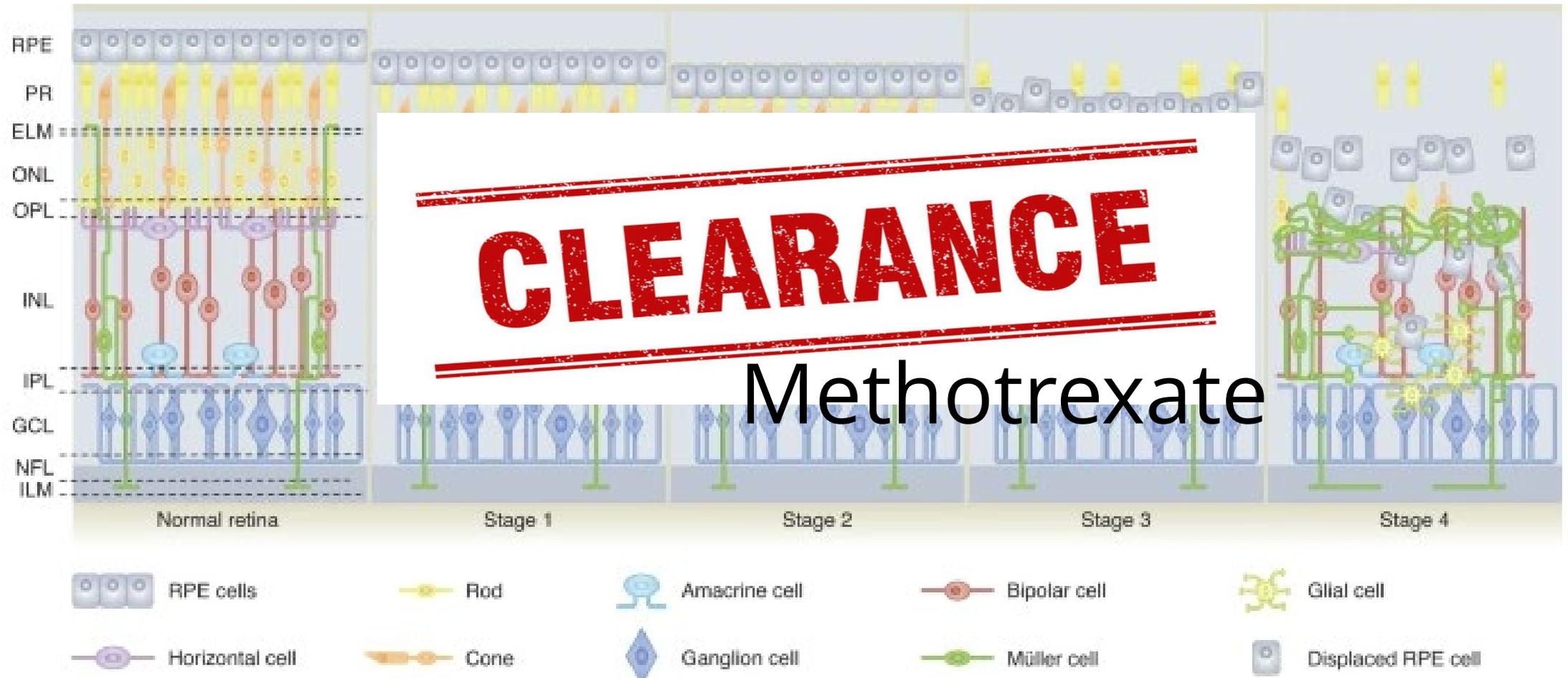
- **Many mutations** associated with retinal degeneration lead to the production of **misfolded proteins** by cells of the retina.
- These abnormal proteins **cause cell death** by activating the Unfolded Protein Response, a set of conserved intracellular signaling pathways that detect protein misfolding **within the endoplasmic reticulum** and control protective and proapoptotic signal transduction pathways.



**CLEARANCE**

Methotrexate

# A therapy according to the stage



•Review Article Published: 31 January 2022 **Bioengineering strategies for restoring vision**

•[Jasmina Cehajic-Kapetanovic](#), [Mandeep S. Singh](#), [Eberhart Zrenner](#) &

•[Robert E. Maclaren](#) *Nature Biomedical Engineering* volume 7, pages387–404 (2023)

# **Vision Sciences Living in Momentum**

**Genetic testing interpretation can be complex**



# **ARVO 2024 Seattle, WA**

**Register now**



Ramiro  
Maldonado  
(Duke)

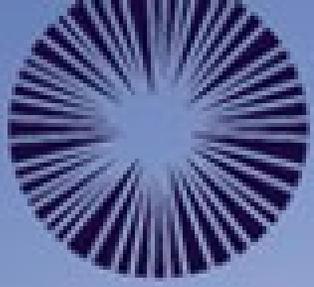


Robert  
Hufnagel  
(NIH)



Kristy  
Lee  
(UNC)

**Interpreting genetic tests: The basics of molecular diagnosis through application of results**



AMERICAN ACADEMY™  
OF OPHTHALMOLOGY

**AAO course 2024**

# Game of Genes



# ERG in children Workshop



**AAPOS 2024**  
AUSTIN ★ TEXAS



A person in a light green jacket and dark pants is running across a blue-painted wall. The wall features various murals, including a large hand, a face, and a boat. The scene is lit with a strong blue light, creating a dramatic and hopeful atmosphere.

There is a bright  
future for patients  
with IRDs

There is progress... there is HOPE

# Thank you!



Ramiro.Maldonado@duke.edu



@RamMaldonado32



ramiro-s-maldonado-md



[ramiro.maldonado@duke.edu](mailto:ramiro.maldonado@duke.edu)

 **Duke Center for Ophthalmic Genetics**  
Duke University School of Medicine





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**Todd C. Brady, M.D., Ph.D. Chief Executive Officer**

# Phase 2 Clinical Trial of ADX-2191 in Retinitis Pigmentosa

ADX-2191 has the potential to be the first approved drug for retinitis pigmentosa, a clinical group of rare genetic eye diseases.

Retinitis pigmentosa refers to a group of inherited retinal diseases characterized by cell death and loss of vision.



- Retinitis pigmentosa **affects more than 1 million people** worldwide. Mutations leading to rhodopsin misfolding account for approximately one-third of cases.
- There is **no approved therapy** for retinitis pigmentosa.
- **U.S. FDA Orphan Drug Designation** for ADX-2191 for the treatment of retinitis pigmentosa was granted in August 2021.



**Preclinical electroretinographic evidence** in a P23H rhodopsin mutation mouse model of retinitis pigmentosa **suggests that methotrexate improves retinal function.**

ADX-2191 (methotrexate injection, USP) for intravitreal administration is an investigational drug candidate. Sources: Aldeyra internal estimates; FASEB J. 34(8): 10146-10167, 2020. PBS = phosphate-buffered saline. MTX = methotrexate.

# ADX-2191: Phase 2 Clinical Trial Design in Retinitis Pigmentosa

## Design

Single-center, dose-ranging, open-label clinical trial of ADX-2191 (400µg methotrexate in 0.05mL) in patients with retinitis pigmentosa

## Inclusion Highlights

Diagnosis of retinitis pigmentosa due to rhodopsin gene mutations, including P23H

## Dosing Regimen

### Cohort A (n = 4):

Monthly injections of ADX-2191 for three months

### Cohort B (n = 4):

Twice-monthly injections of ADX-2191 for three months

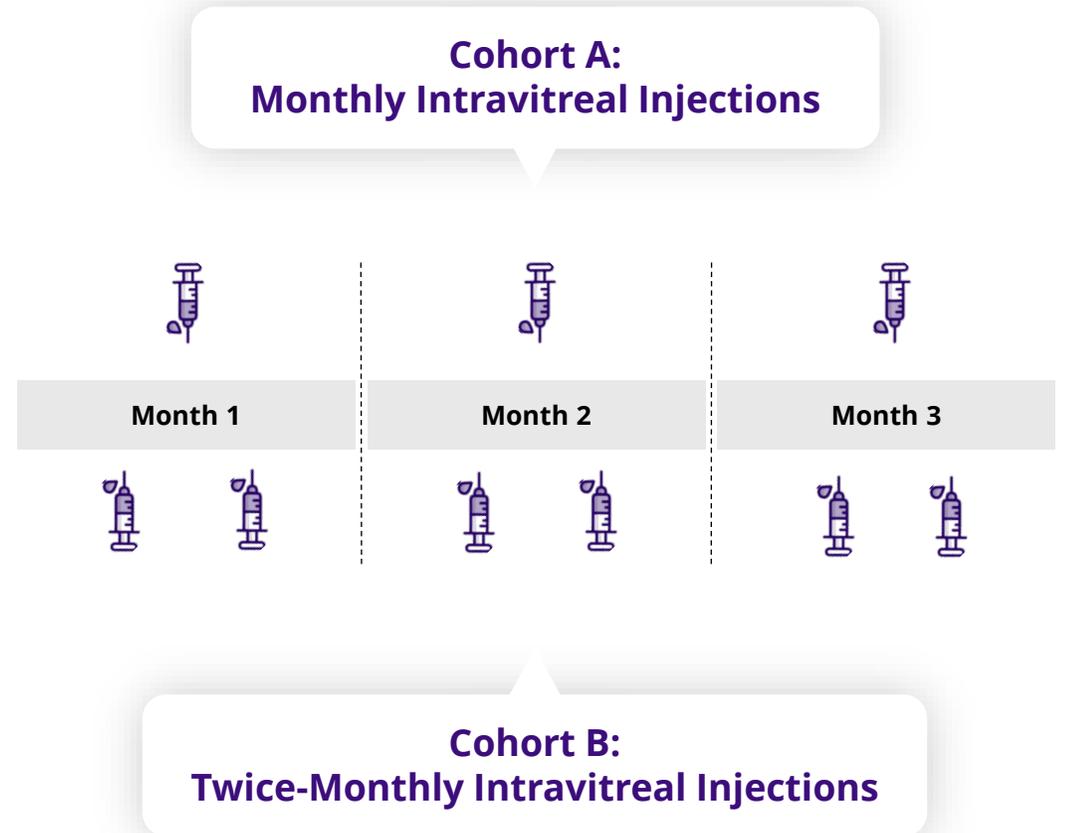
## Primary Endpoint

Safety and tolerability

## Secondary Endpoints

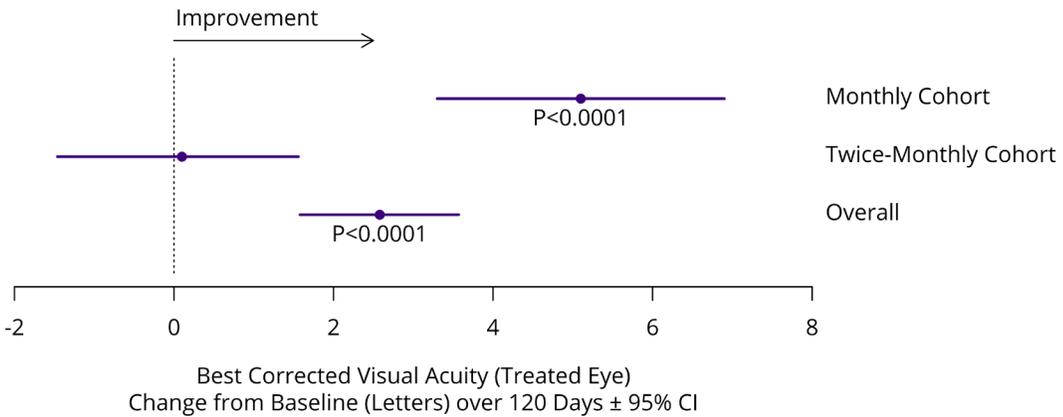
1. Best corrected and low-light visual acuity
2. Macular retinal sensitivity as assessed by MAIA perimetry
3. Dark-adapted flash analyzed by ERG
4. Peripheral retinal sensitivity as assessed by DAC perimetry
5. Retinal morphology as assessed by OCT

**Acuity, perimetry, and OCT assessments were performed monthly for four months from initiation of therapy. ERG was performed at baseline and at 90 days from initiation of therapy.**

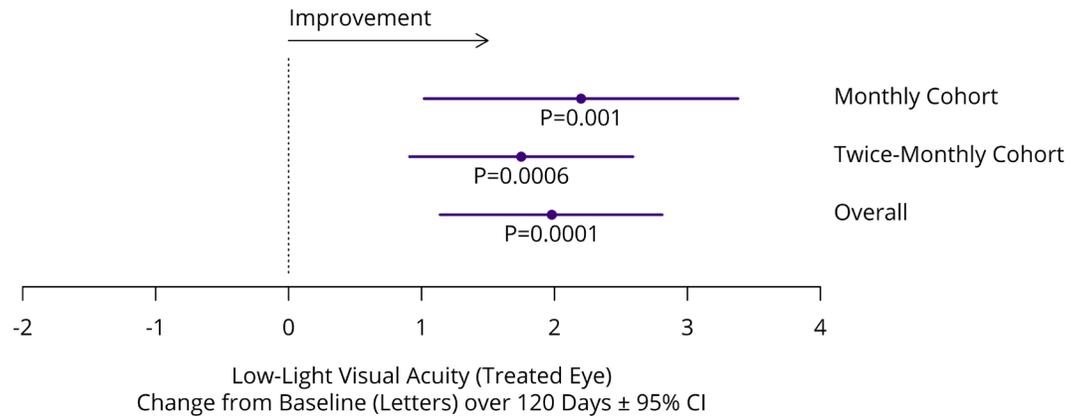


# Statistically Significant Improvement in Visual Acuity Observed in the Retinitis Pigmentosa Phase 2 Clinical Trial

## Normal Lighting

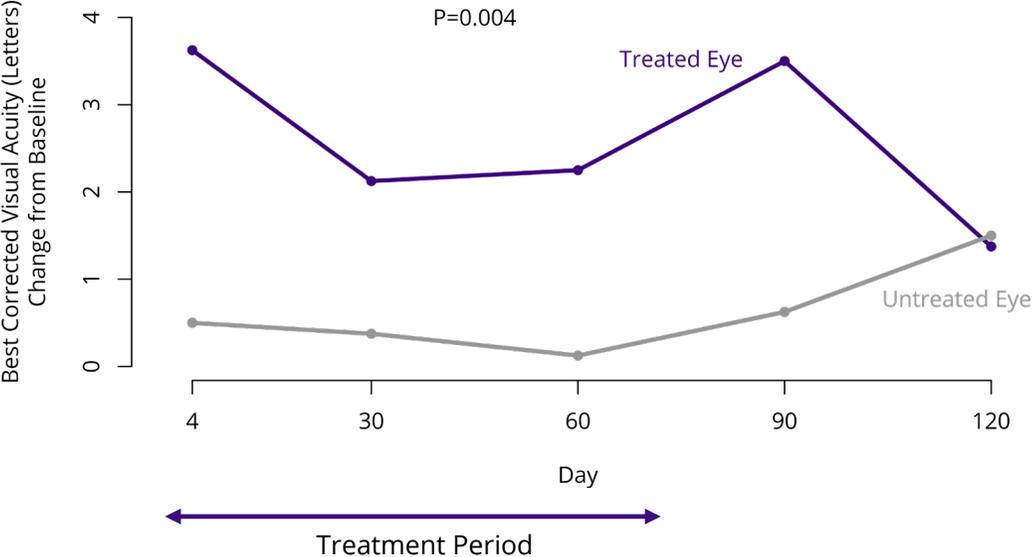


## Dim Lighting

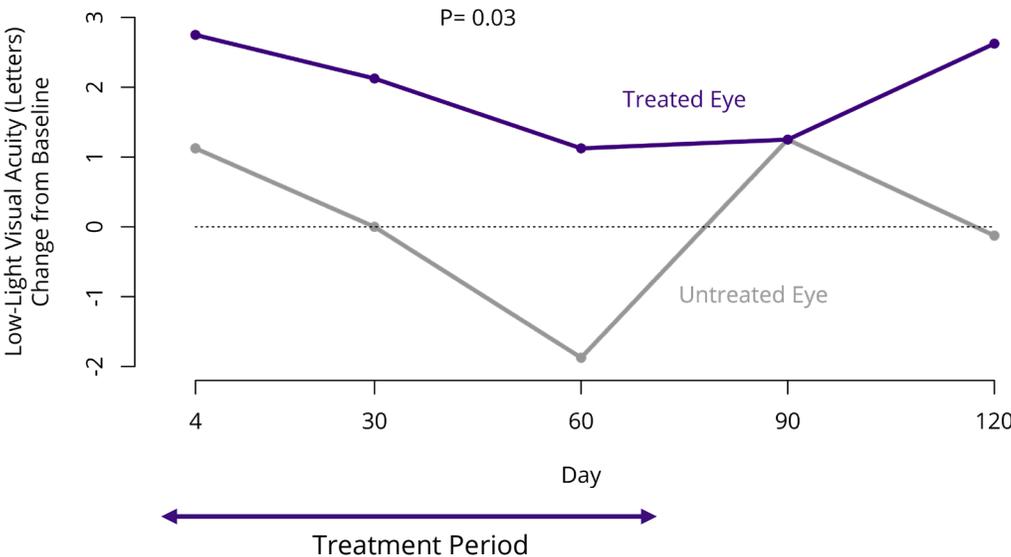


# In the Retinitis Pigmentosa Phase 2 Clinical Trial, Visual Acuity in ADX-2191-Treated Eyes Was Superior to that of Untreated Eyes

## Normal Lighting



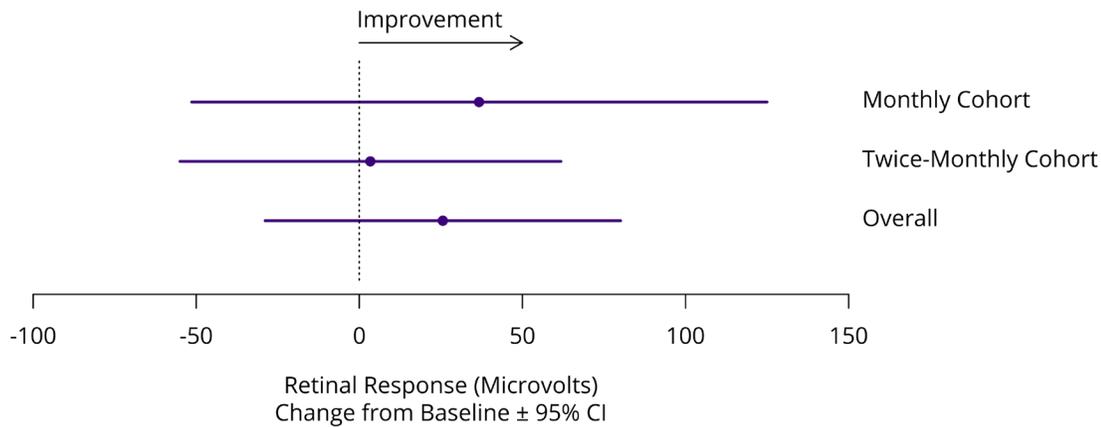
## Dim Lighting



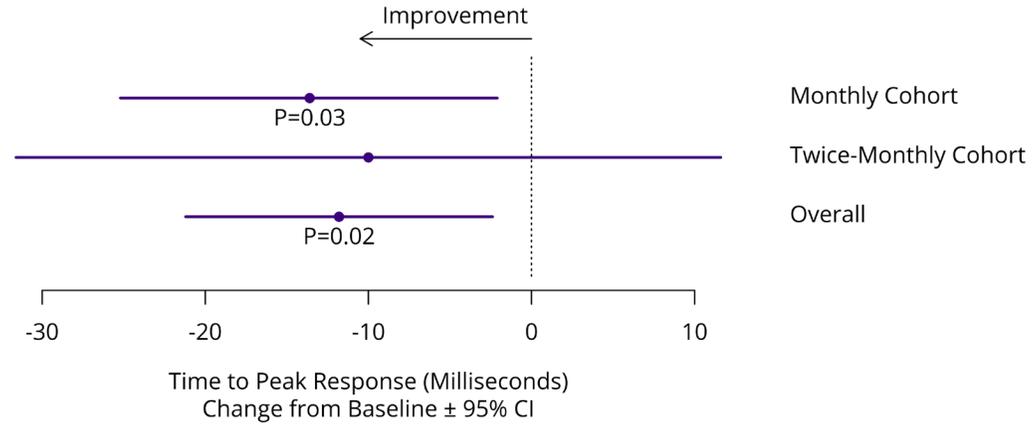
ADX-2191 (methotrexate injection, USP) for intravitreal administration is an investigational drug candidate. Data derived from mixed model for repeated measures of both dosing cohorts with baseline, day, dose, and treatment eye as factors.

# As Assessed by ERG, Retinal Function Improved in the Retinitis Pigmentosa Phase 2 Clinical Trial

## Peak Response

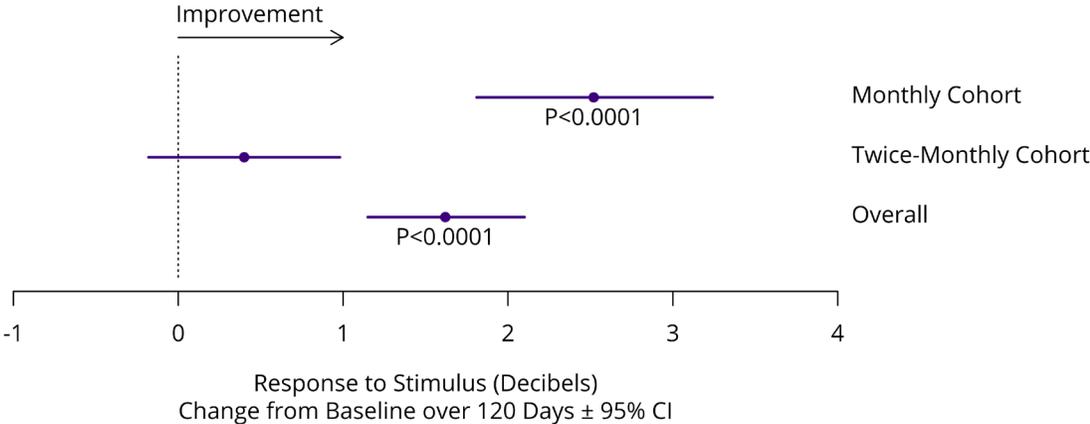


## Time to Response



# As Assessed by MAIA Microperimetry, Statistically Significant Improvement in Retinal Sensitivity Observed in the Retinitis Pigmentosa Phase 2 Clinical Trial

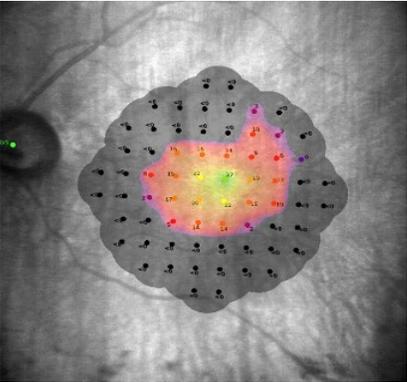
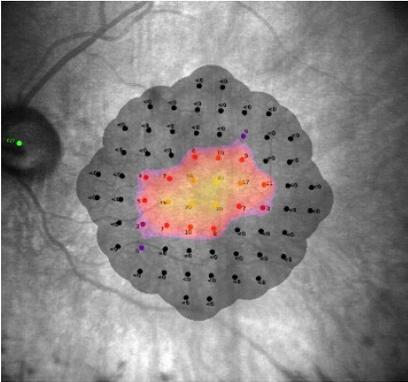
## Retinal Sensitivity



## Illustrative results from an enrolled patient indicate central and peripheral improvement in macular retinal sensitivity

Baseline

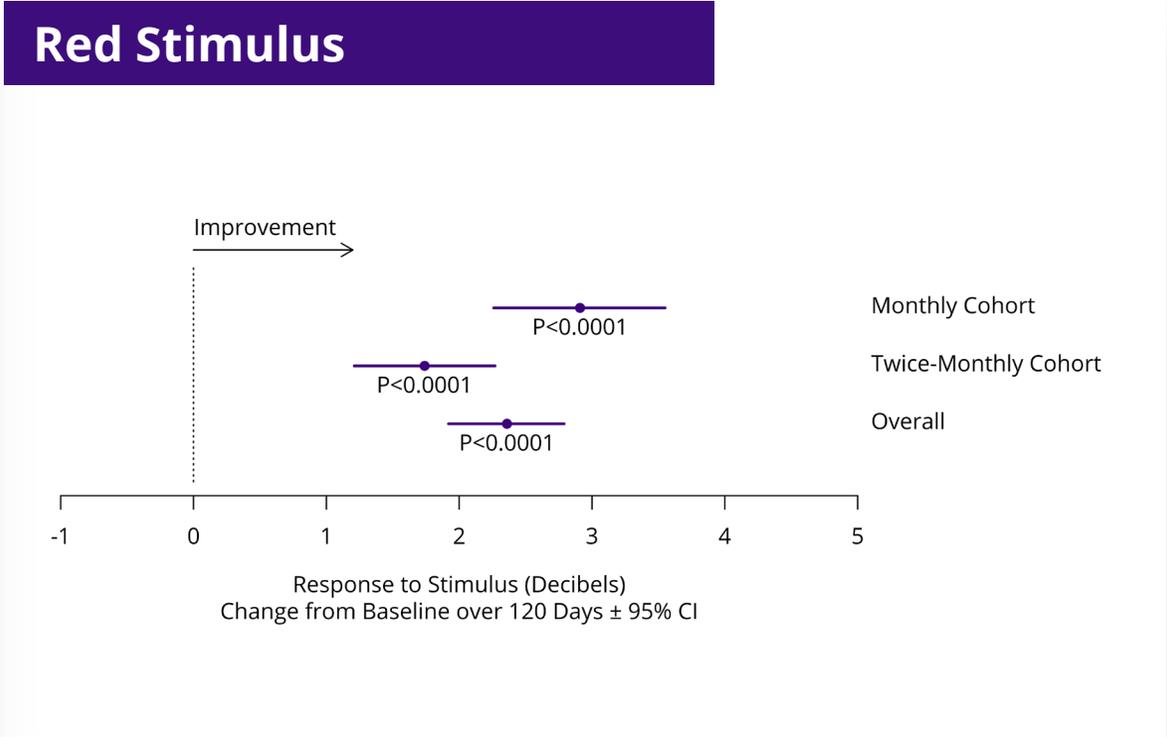
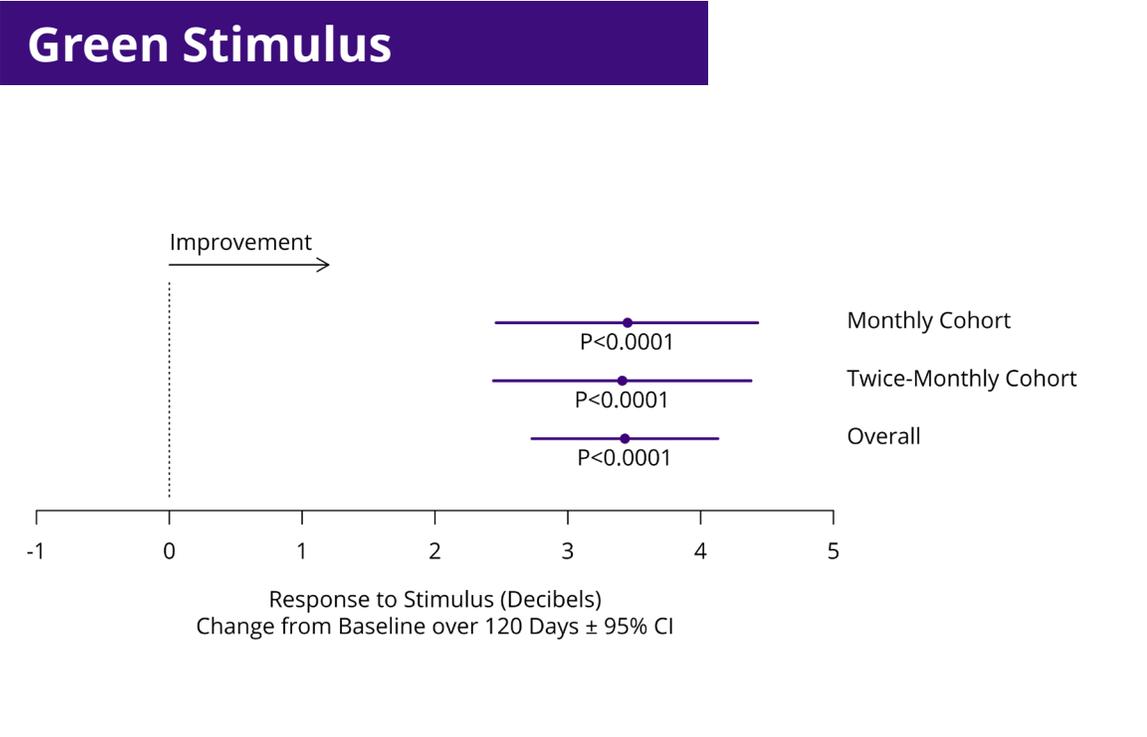
Day 90



ADX-2191 (methotrexate injection, USP) for intravitreal administration is an investigational drug candidate. Baseline retinal sensitivity was approximately 50% higher in the twice-monthly dosing cohort than in the monthly dosing cohort. Data derived from mixed model for repeated measures with baseline, day, and dose (if applicable) as factors. Retinal sensitivity assessed where non-zero sensitivity losses were  $\geq 7$  decibels from nearest concentric assessment. MAIA = Macular Integrity Assessment. CI = confidence interval.



# As Assessed by DAC Perimetry, Statistically Significant Improvement in Retinal Sensitivity Observed in the Retinitis Pigmentosa Phase 2 Clinical Trial



# Planned Phase 2/3 Clinical Trial of ADX-2191 in Retinitis Pigmentosa

<b>Design</b>	Randomized, double-masked, clinical trial
<b>Dosing</b>	40 µg vs. 400 µg administered monthly for 12 months
<b>Size</b>	30 retinitis pigmentosa patients with rhodopsin mutations, randomized 1:1
<b>Primary Endpoint</b>	Peripheral vision sensitivity to green (rod-mediated) light under dimly lit (scotopic), dark-adapted conditions
<b>Other Endpoints</b>	Best-corrected and low-light visual acuity, safety

**Clinical trial initiation expected in H2 2024<sup>†</sup>**



<sup>†</sup>The timing of clinical trials depends, in part, on the availability of clinical research facilities and staffing, the ability to recruit patients, and the number of patients in the trial.

The background features a complex network of glowing white nodes and lines, resembling a molecular structure or a data network. The nodes vary in size and brightness, and the lines connect them in a web-like pattern. The overall color scheme is a gradient of purple, from dark on the left to light on the right.

aldehyra

Questions



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**Todd C. Brady, M.D., Ph.D., Chief Executive Officer, Aldeyra Therapeutics**

# Pipeline and Milestone Review



# Clinical and Regulatory Milestones



ReproXalap



## Allergic Conjunctivitis

Positive Phase 3 INVIGORATE 2 trial top-line results announced



## Dry Eye Disease

Proposed clinical trial top-line results and potential NDA resubmission expected in second half of 2024, pending clinical trial results, feedback from ongoing FDA discussions, and other factors<sup>† ‡</sup>



ADX-629



## Sjögren-Larsson Syndrome

Phase 2 clinical trial top-line results announced\*



## Moderate Alcohol-Associated Hepatitis

Open-label Phase 2 clinical trial results expected H2 2024<sup>‡</sup>



ADX-246



## Atopic Dermatitis

Phase 1 clinical trial initiation expected in H1 2024<sup>‡</sup>



## Metabolic Disease

Pre-clinical program initiated



ADX-248



## Dry Age-Related Macular Degeneration/Geographic Atrophy

IND expected to be submitted in 2024



ADX-2191



## Retinitis Pigmentosa

Phase 3 clinical trial initiation expected in H2 2024<sup>‡</sup>

<sup>†</sup>Regulatory review and discussion timelines are flexible and subject to change based on the regulator's workload and other potential review issues. <sup>‡</sup>The timing of clinical trials depends, in part, on the availability of clinical research facilities and staffing, the ability to recruit patients, and the number of patients in the trial. \*Investigator sponsored.



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**Todd C. Brady, M.D., Ph.D., Chief Executive Officer, Aldeyra Therapeutics**

# Concluding Remarks